VETERANS' ADMINISTRATION'S RESEARCH EFFORTS ON NEUROLOGICAL DISORDERS

HEARING

BEFORE THE

SUBCOMMITTEE ON
HOSPITALS AND HEALTH CARE

OF THE

COMMITTEE ON VETERANS' AFFAIRS
HOUSE OF REPRESENTATIVES

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VETERANS' ADMINISTRATION'S RESEARCH EFFORTS ON NEUROLOGICAL DISORDERS

THURSDAY, APRIL 26, 1984

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HOSPITALS AND HEALTH CARE,
COMMITTEE ON VETERANS' AFFAIRS,
Washington, DC.

The subcommittee met, pursuant to notice, at 9:07 a.m., in room 334, Cannon House Office Building, Hon. Bob Edgar (chairman of the subcommittee) presiding.

Present: Representatives Edgar, Evans, Penny, Staggers, Rowland, Hammerschmidt, Bilirakis, and Johnson.

OPENING STATEMENT OF CHAIRMAN EDGAR

Mr. EDGAR. Good morning. The subcommittee will come to order.

Before we begin the hearing, I would like to acknowledge the announced retirement of Dr. Donald L. Custis, Chief Medical Director of the Veterans' Administration, which will become effective May 13, 1984. Dr. Custis has had a long and illustrious career in Federal service, with 32 years in the Navy and 8 years in the Veterans' Administration. He is the only person to have ever headed two major health agencies at the U.S. Government, having served as the Surgeon General of the Navy as well as the VA's Chief Medical Director.

I personally feel that I, my colleagues on the subcommittee, and especially the veterans of this country, will experience a great loss when Dr. Custis leaves his leadership role in the largest health care delivery system in the free world. The doctor's innovative executive abilities are well reflected in the strategic management systems he had put in place in the Department of Medicine and Surgery, which include the medical district planning process, resource allocation plans, and the decentralized hospital computer plan.

Dr. Custis can take great pride in his dedication to our country and our Nation's veterans. I am certain we will all miss his creativity and we will miss him greatly.

This is the first in a series of three hearings dealing with the VA's medical research. Additional hearings are scheduled for May 8 and June 13. We are meeting this morning to provide the subcommittee and the public with information concerning the Veterans' Administration's research efforts on neurological disorders. It has been said that "research is a way to keep you moderately dissatisfied with what you have", and since we are extremely desirous

of improving health care for veterans, we want to learn what the VA is doing in their research programs.

As you know, the VA's medical research program is authorized by Congress to promote high quality health care for our Nation's veterans by offering research opportunities to practicing clinicians as well as research specialists. Such opportunities attract high-quality staff and promote high quality health care.

Since the VA's medical research budget is almost $200 million annually, we want to be certain that these funds are expended on worthwhile projects. We want to hear from the VA on how they manage the research program, and the subcommittee members are looking forward to seeing demonstrations of some of the VA's research projects.

I personally believe that the VA's research program is outstanding and that the public should be aware of the many accomplishments of VA researchers. For example, two VA scientists received Nobel Prizes for medicine in 1977. VA scientists have received awards for research on hypertension, discovery of leukemia and cancer-inducing viruses in animals, development of the concept of the CAT scanner, as well as the development and perfected treatment such as compensatory speech for those whose tongues have been excised, gestural language for the speechless, and kinetic communication for blind persons who are also deaf.

Our subcommittee visited each of the VA's six medical regions last year, and during those visits we were privileged to view some of the exciting research being conducted at VA medical centers. For this reason, in addition to those mentioned above, I believe the Congress as well as the public should be aware of the VA's research efforts, since those efforts have enriched the quality of life, not only for veterans, but also the general public.

I would now like to recognize the ranking minority member of the subcommittee, the Honorable John Paul Hammerschmidt of Arkansas.

OPENING STATEMENT OF HON. JOHN PAUL HAMMERSCHMIDT, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF ARKANSAS

Mr. HAMMERSCHMIDT. Thank you, Mr. Chairman.

I certainly want to join with you in commending the efforts of Dr. Donald Custis, who has announced his decision to retire as the Chief Medical Director of the Veterans' Administration. In war and peace, Dr. Custis has made vast contributions to his country. He is a noted surgeon as well as an exceptional medical educator. His outstanding talents as an administrator were responsible for his selection as Surgeon General of the Navy and from there to the office he now leaves. His appearances before this committee have always been exemplary. His wisdom and expertise and his valuable advise and counsel have been of material assistance to all of us and he will be sorely missed.

Mr. Chairman, Dr. Custis can take great pride in the fact that he takes into retirement the love, affection, and respect of 220,000 VA medical employees. He has led them with distinction and grace and I complete associate myself with your remarks, Mr. Chairman, con-

cerning the loss we all feel at his departure. We wish him the very best as he enters a well-earned retirement.

Mr. Chairman, I congratulate you on the hearings you have scheduled on VA research. VA's effort in medical care for veterans is greatly enhanced by what it does in medical education and medical research. This threesome joins hands to ensure the quality care that we all want our veterans to receive. Our committee has always recognized this and that is why we have always supported care, education, and research as an indivisible entity.

Mr. Chairman, research in the VA is a big success story. You have noted a number of these successes in your opening statement. We would both agree that VA researchers deserve our highest commendation. We would also agree that much more needs to be done. I am sure our witnesses this morning will enlighten us on what has happened in the past and what perhaps we can look forward to in the future. I am anxious to hear their testimony.

Mr. Chairman, I know you want to make this formal introduction, but while I have the floor, I want to say how particularly pleased and honored I was to have met our first witness of the morning, Dr. Albert Sabin. Mr. Chairman, I join you in welcoming him to our committee.

Mr. EDGAR. Thank you, John Paul.

Before I introduce our first witness this morning, I would like to make special note of another event that is taking place in the committee. Vance Gilliam, our committee bill clerk, will be retiring from the committee. Vance, we are really sorry to see you leave. Vance is a World War II veteran and he was a VA employee for 20 years. He has been with the committee for 15 years. He is going to retire on April 30. He served under four chairmen—Olin Teague, William Jennings, Bryan Dorn, Ray Roberts, and Sonny Montgomery.

I wonder if all of you will join me in a round of applause for his leadership.

[Applause.]

Mr. EDGAR. We are real pleased to have all of you here today, and we are very honored to have as our first witness this morning Dr. Albert Sabin, who is a pioneer in the field of protective vaccines for viruses causing fatalities and crippling illness. All of us remember that Dr. Sabin had devoted much of his life to the study of poliomyelitis—and we will let Dr. Sabin pronounce that for us correctly. [Laughter.]

But the most notable achievement is the development of the oral polio vaccine, which can be stored indefinitely in a deep freeze, produced inexpensively, and promises a lifetime of immunity from the dreaded disease of polio.

Dr. Sabin, we welcome you to our committee this morning. We are really honored to have you here participating. We are particularly honored that you have taken the time in your testimony, which I have had a chance to review, to go into some detail of your personal feelings and views. We are pleased to see you and have you participate.

Dr. ROWLAND. Mr. Chairman, would it be out of order if I asked that we applaud Dr. Sabin.

Mr. EDGAR. No, I think that would be in order.

[Applause.]

STATEMENT OF ALBERT B. SABIN, M.D., EMERITUS DISTINGUISHED SERVICE PROFESSOR, UNIVERSITY OF CINCINNATI, AND EMERITUS DISTINGUISHED SERVICE PROFESSOR, MEDICAL UNIVERSITY OF SOUTH CAROLINA

Dr. SABIN. Mr. Chairman, members of the committee: I appreciate your invitation to testify at this hearing on research on neurological disorders by the Department of Medicine and Surgery of the Veterans' Administration.

In your letter of invitation you specifically asked me to comment on three points: One, the value of medical research in the development of clinical treatment modalities; two, a historical perspective of my own research efforts; and three, to give my personal thoughts and impressions from the viewpoint of a person who has experienced a debilitating illness.

For the record, let me say that I am 77 years old and am now retired, not only because of age, but also because of a nearly fatal, extensive paralytic illness during the past year, from which I have made a remarkable, though not yet complete, recovery.

I have spent my life in full-time research on infectious diseases and virology, especially as related to paralytic poliomyelitis—that's poliomyelitis, Mr. Chairman—[Laughter], and other diseases of the nervous system. I have had the good fortune to develop the oral vaccine that has been used for the prevention of polio for more than 20 years throughout the world. I am also a World War II veteran and for many decades served on the Armed Forces Epidemiological Board and on NIH study sections and councils dealing with research grants.

And now, Mr. Chairman in response to your first question, let me say that no clinical treatment modalities can be developed without appropriate research. But having said what is self-evident, the real question that must be addressed and answered is what is "appropriate research", and research on what, by whom, where, and the bottom line as far as it relates to this particular congressional subcommittee is how much money should the Veterans' Administration spend on specific items of research in relation to expenditures by other Federal agencies on the same problem.

Of the various neurological disorders of special importance to the VA, I chose to comment only on spinal cord injury paralysis, SCI paralysis for short. The reason for my choice is that during the months I recently lay extensively paralyzed and utterly dependent on the help of others, I came to appreciate more than ever before the plight of the many thousands who become paraplegics or quadriplegics each year following injuries to the spinal cord and who then remain paralyzed for the rest of their life. Again, for those who would need a definition, paraplegics in general would be paralysis below the waist, and quadriplegics below the neck.

Moreover, after I began to recover from my own paralytic illness which resulted from a disease of the nerves outside of the spinal cord, several private organizations concerned with doing something about the ongoing misery of spinal cord injury paralysis asked for my support of their work. After familiarizing myself with the

status of current research on SCI paralysis, I declined to support the work of private organizations that based their fund-raising activities on unwarranted hopes for imminent "cures."

In connection with the present hearing, I tried first of all to obtain the best possible estimate of the magnitude of the problem of spinal cord injury paralysis, that is, the number of all persons afflicted in the United States and the number of afflicted veterans who required prolonged care in VA hospitals. The best available estimate—and it is still only an estimate—is that the total number of persons with persistent paraplegia or quadriplegia—I emphasize persistent—caused by injury to the spinal cord in the United States is about 200,000, and that about 10,000 additional persons are paralyzed each year.

I am indebted to Dr. Hollis G. Boren, Assistant Chief Medical Director for Research and Development of the Veterans' Administration, for providing me the information prepared by Andrew J. Copperthite on the magnitude of the problem in VA hospitals.

During the period of fiscal year 1976 through 1982, a total of 18,218 individual SCI patients were treated in VA facilities. Many of these came several times a year, so that the total number of admissions during the year for this condition was closer to 70,000. But the individual number of veterans who came for help was 18,218, treated in VA facilities which, as of September 30, 1983, included 19 spinal cord injury centers with a total operating bed capacity of 1,353. Among the 18,218 individual patients, 38.7 percent had service-connected spinal cord injury paralysis. The others were like many thousands of others in the United States who needed help, who were veterans. Thus, while this tragic, traumatic neurologic disorder represents a major ongoing problem for VA facilities, it is evident that the total number of service-connected and nonservice-connected patients with this disorder constitute less than 10 percent of the estimated total number in the United States.

My point is that this catastrophic neurologic disorder is not specifically a VA problem—and there are specific VA problems—but this particular thing is not specifically a VA problem but, rather, a national problem, and the research that must be carried out is a national responsibility. It may be asked, therefore, whether the Federal Government should provide funds especially designated for research on this catastrophic problem through more than one agency—for example, through the National Institute of Neurological and Communicative Disorders and Stroke of the National Institutes of Health and through the Veterans' Administration—or whether the cause of the acquisition of relevant new knowledge would be better served if the funds would be provided through only one agency. Duplication of effort is sometimes necessary, but at other times it can be wasteful and undesirable.

The question should perhaps also be asked whether current research on spinal cord injury paralysis is commensurate with what the state-of-the-art now permits—and this is very important. I digress for a moment. You can ask a thousand questions as a researcher, but if the state-of-the-art at the particular moment does not permit you to get an answer, then you have got to concentrate on those questions that the state-of-the-art permits or whether it is insufficient because of lack of funds and whether the effort is being

diluted too much by work on general biological questions that may, like much other knowledge, be worthwhile but only remotely relevant.

I want to digress again and say that there are thousands of questions one can ask of nature, and sometimes you don't know which one may be really important. But to take money that is designated for research on spinal cord injury paralysis and under that umbrella do all sorts of things that may only be very remotely related is, from my experience of more than half a century, perhaps not the best way to do things.

In my judgment, research that is specifically relevant to spinal cord injury paralysis should be designated to obtain the knowledge needed to answer the following three questions:

One, how much more can be done, during the first hours after injury, than is being done now to prevent—I emphasize to prevent—the development of subsequent permanent paralysis, especially since in most instances the spinal cord is only bruised and not severed? I am personally inclined to believe that the best hope for the future lies in studies on prevention during the first hours of injury.

Second, can anything ultimately be done for those paraplegics and quadriplegics past the acute phase to restore the interrupted nerve tracts in the spinal cord to a point of normal function? There are certain things that can and should be done along these lines, especially to discover why the nerve fibers outside the spinal cord—even though the nerve cells are inside the spinal cord—why the nerve fibers outside the spinal cord can regenerate after injury, while those that are ruptured or scarred inside the spinal cord cannot or do not.

Here it seems to me necessary to stress the importance of an appropriate experimental model for the human paraplegic condition. Because what happens in a goldfish does not happen in a rat, and what happens in a rat may not happen in a cat, and what may happen in a cat may not happen in an upright monkey, and what happens in an upright monkey may be the closest we can get to the human bruised or severed spinal cord. It seems utter folly to me to choose to work in rats and cats simply because there isn't enough money to do the necessary experiments in monkeys. The expression "regeneration research" has in the last few years come into wide use to describe a great deal of the work being done in this particular field. But, in my judgment, much of it is way off the target of restoring the continuity of the disrupted nerve fiber tracts in the injured spinal cord.

While the research on restoring paraplegics and quadriplegics to normal function does not, at least to me, seem very promising—and not only to me, but to many others—there are certain things that can and should be done, but the effort should not be diluted by research on the interesting general biological problem of regeneration, much of which, at best, is only remotely relevant to spinal cord injury paralysis. I know that it is not always easy to decide on what is relevant and what is not relevant, but to call everything relevant dangerously dilutes the necessary work in problem-oriented research activities.

Now, the third question, is new knowledge needed for optimum rehabilitation and care of spinal cord injury patients? The research needed in this area is best identified and carried out in spinal cord injury paralysis centers of which the Veterans' Administration now has 19.

Dr. Murray Goldstein, Director of the National Institute of Neurological and Communicative Disorders and Stroke, informed me that $21.1 million was allotted specifically for spinal cord injury research for this fiscal year, which represents approximately 6 percent of the Institute's total budget for research on various neurologic disorders. The $21.1 million is subdivided into $14.1 million for research on so-called "regeneration of the spinal cord," and $7 million on other aspects of spinal cord injury. During the period of 1978 to 1984, inclusive, a total of $68 million has been allocated for research on spinal cord regeneration. I do not have the information to comment on whether this amount of money that has been spent and is being spent on spinal cord injury research is too little, too much, or just right. But I think it is important to try to find out whether it is, at least by the best available criteria that we can use, very specific criteria.

I'm sorry, but permit me, Mr. Chairman, to make another digression. I have heard a lot of philosophic discussions about research during my life, and one of them that keeps recurring is that the best way to get things done is to find a good man—as if he carries a label on his forehead—find a good man, give him what he needs, and for Heaven's sake, leave him alone. In my judgment, that is not the best way to carry out problem-oriented research. There is a great need for subdividing effort, division of labor in the effort, in all things that are very complex. But to just say, "Here's the money, come and get it and do the best you can," that's not the best way to do it.

I don't know, for example, how much the Veterans' Administration is spending on what might properly be designated as spinal cord injury research.

It does seem to me, however, that Federal expenditures on research, aiming at the maximum possible prevention of spinal cord injury paralysis—I said "prevention"—and at the remote possibility of restoring some measure of normal function to those already paralyzed by spinal cord injury can best be coordinated—and coordination is badly needed in problem-oriented research—by providing funds to qualified investigators through a single agency.

Based on the reports I have seen in the scientific literature, the Veterans' Administration already has many highly qualified investigators working on this subject who are already receiving research funds from the National Institutes of Health and who should be able to compete successfully with qualified investigators in other academic institutions for research funds in the future. I have never seen any merit in several agencies supporting the same research project, except under very special circumstances.

Although my own research efforts have not dealt at any time with the problem of spinal cord injury paralysis, my work on paralytic polio, which started 53 years ago, may have some parallels. First of all, the problem of paralytic polio could be dealt with only by preventing the irreversible destruction of the large number of

motor nerve cells, and the work on prevention was long delayed by an erroneous conception of the nature of the human disease based on misleading experimental models of the disease in monkeys. Moreover, the salaries of responsible investigators and the research facilities were provided by the institutions in which they worked, while the research funds came from a single agency that coordinated the total effort. Spinal cord injury paralysis is totally different from paralytic polio, but the organization of the research effort on spinal cord injury paralysis may benefit—it may, I don't know—from the polio experience.

Mr. Chairman, my testimony may not have given you what you wanted, but I hope it is not totally irrelevant. Thank you very much.

Mr. EDGAR. Thank you very much for your statement and your clarity of thought. It was very helpful to us on this committee.

I failed to mention before the introduction that your wife has also joined you here this morning. I would like to make recognition that Mrs. Sabin is also in the audience and we thank her for being here.

Dr. Sabin, I am going to save most of my questions for the end, after I let my colleagues do the questioning. But I did want to ask just a general, basic question first which is not targeted to your statement but targeted to the whole question of research in general.

Last night, at a meeting of a group I organized, called the Futures Advisory Board, we had about 25 individuals sitting around a room talking about research and development generally and the commitment of the Federal Government to research. There was some concern in that room that with the commitment that we have made to defense expenditures over the next 5 years, spending $2 trillion on defense, and some of the areas of research and development being cut back in the Federal budget in some of the domestic areas, that there was deep concern that perhaps we were putting our emphasis in the wrong areas by emphasizing defense at the expense of a lot of other areas of research.

With your experience in your research in the polio area and in the modeling that you set up to come to your conclusions, can you talk for a moment just about research and development in general and its importance to the whole society in which we live, in terms of not just health care but other areas of concern?

Dr. SABIN. Let me see how briefly I can comment on this.

Mr. EDGAR. We'll try to keep you under 2 hours.

Dr. SABIN. No. 1, the objective of all research and development is to get new knowledge that is not available now in order to be able to do certain things that urgently need to be done that we cannot do now. There are different kinds of things that are needed in the complex world that we live in for which research and development is very important and can give us knowledge that we don't have. Some of it has to be general knowledge which applies to everything; whether it be in mathematics, biology, physics, chemistry, it applies to everything. It doesn't specifically apply to cancer or spinal cord injury paralysis or things like that, but that knowledge is important.

Now, it seems to me that it is very important not to confuse the requirements of problem-oriented, problem-solving oriented research specifically and the research which needs to be done to give us general knowledge which we don't have now, because otherwise too many of my colleagues have a tendency to turn and do the easy things under the big umbrella of basic research. They say, yes, there is some relationship to the specific problem for which a solution is needed. But problem-oriented research, of which there are many things, and for which the Congress has set up the National Institutes of Health specifically, with the exception of one Institute, the Institute of General Medical Sciences, must deal very definitely with coordinated research on very specific questions, and always to ask how does this knowledge relate to our problem.

For example, I have a book here that has been published, edited by Dr. Seil of Portland, OR on nerve organ and after tissue regeneration research. I particularly looked there to see how many of the activities are relevant to, let's say, spinal cord injury research. There are many more head injuries than spinal cord injuries.

I also wanted to see whether at the end of this symposium there was any attempt made and then recorded in here as to how each one of the particular research projects relate to spinal cord injury problems. Never mind that you can replace some nerve cells which may be useful in Parkinson's disease. It's another business altogether than spinal cord injury research, where you've got tracts severed or bruised.

Well, my point is that you cannot speak of research and development in general terms, nor can I say at any time, without an actual examination, whether the money that is currently made available is too little, too much, or just right. I think one must deal specifically with each particular problem separately. And besides, as Congressmen, you are concerned, if I may make this statement, you are concerned with all sorts of national problems. And when there is just so much money to spend, you have got to make some decision, however difficult it may be, in saying so much for this and so much for that. So if you ask me whether the statement that is so often heard, that so much money is being spent on defense, that other research and development efforts that are of vital importance to the nation maybe underfunded, I don't know whether it is or is not.

Mr. EDGAR. Thank you very much.

I yield to my colleague, John Paul Hammerschmidt.

Mr. HAMMERSCHMIDT. Thank you, Dr. Sabin, for your very lucid and interesting testimony.

In your graphic reference to goldfish, rats, cats, and monkeys, you indicate, if I interpret correctly, that it may be folly to use money in the spinal cord research area to experiment with rats and cats just because not enough money is available to experiment with monkeys.

Some of us on this subcommittee, in making a round of the VA regions last year, visited Palo Alto. There we witnessed some research on spinal cord regeneration. There was a fish, the only known species, I guess, that regenerates—and you're probably familiar with that. You may not be able to comment on my question, but I am wondering if what they are doing there is relevant.

Dr. SABIN. This is a decision that has to be an in-house decision. I would say, offhand, that the high priority must be on whether a given maneuver or a given procedure that the present state-of-the-art permits can be achieved, in the spinal cord of an upright monkey whose spinal cord has been bruised or severed, to compare with that which happens in human beings.

The general knowledge of regeneration in a fish or in a newt or other areas of the central nervous system should perhaps come from other areas of research. We can't do everything. There must be division of labor. And those who have the responsibility to deal with spinal cord injury research, I say stick to your last, and if you cannot do anything else, just let that money go somewhere else. Let the National Foundation support neurosciences. After all, the Neurological Institute of the National Institutes of Health is spending only 6 percent of its budget on spinal cord injury research because there are many other things to be done. So I don't want to say whether that particular fish research at Palo Alto—it is undoubtedly being done by very excellent people—how closely relevant it is to the main problem of spinal cord injury paralysis.

Mr. HAMMERSCHMIDT. Thank you, Doctor.

Dr. SABIN. But it needs to be evaluated. In my judgment, that needs to be an in-house decision. Congressional committees can't make such decisions. But I do believe that this must be an in-house decision, because a very basic principle is involved here. Surely the VA must support research, but what kind, with how much, by whom, on what subjects, I think it may be useful to reconsider those questions.

Mr. HAMMERSCHMIDT. Thank you very much.

I yield my time to my colleagues. Thank you, Mr. Chairman.

Mr. EDGAR. Mr. Evans.

Mr. EVANS. No questions, Mr. Chairman.

Mr. EDGAR. Mr. Staggers.

Mr. STAGGERS. No questions, Mr. Chairman, but I would like to commend Dr. Sabin for his testimony here today and wish him good luck in his complete recovery.

Mr. EDGAR. We have our "resident physician" here, Dr. Rowland, who will now ask some questions.

Dr. ROWLAND. More comments than questions, Mr. Chairman.

I just want to express to you my admiration, as one who remembers the horror in the spring of the year coming in the forties and early fifties. The fear that was in the hearts of parents about their children and polio is all too vividly remembered by me. Of course, first Dr. Salk, and then you with the oral vaccine coming along, and polio becoming a thing of the past. I recall quite well almost every year having at least one patient that developed polio. So I just commend you and express to you my admiration.

Let me ask one question about some research that is going on now in spinal cord injury, and that is the implantation of electrodes in the spinal cord. We do know that below the lesion the nerve tissue continues to function quite well and stimulation with electrodes can cause the function to return.

Can you comment any about what is taking place in that area now?

Dr. SABIN. As I said, I am not an expert in the field. But I would think that the implantation of electrodes which might stimulate certain motor nerve cells a certain amount, this I would put in the category of rehabilitation rather than what needs to be done to supply a lasting return of function by a change in the nerve tracts that go from the top, where you say "I want to move my right leg this way or that way." The tracts which carry that message down to the nerve cells and muscles which are to carry it out are interrupted.

When can you deal with them? Are there things we can do very early to prevent the problems which are similar to that of polio? We realize that the nerve cells destroyed by viruses of poliomyelitis cannot be replaced, and if too many of them are destroyed, we cannot have new nerve cells. Therefore, we had to concentrate on prevention.

It seems to me that I would like to see a lot more research, if it's possible, on prevention during the early period after injury which may not be possible later, because if the spinal cord is only bruised and you still have the pathways and the tracts, there are certain things that might be done there that couldn't be done after 6 months or a year have passed. So I think, as in polio, it may be that prevention, the 10,000 new cases a year approximately that we get in the United States, perhaps one can prevent many of them.

Dr. ROWLAND. I certainly agree with you, that if something could be done to prevent the edema and something to resolve the hemorrhage, so that there was not significant damage done, it would certainly be the way to go in research.

Dr. SABIN. Or even implantation during a certain period when those pathways still have the tract along which the nerve fiber that must get through to other places may still follow a path. You see, I have read the available literature with a very critical eye. I am very sympathetic, you see. I think that research is very important in this field, but how best to do it—Let me repeat, you have many good people in the Veterans' Administration, but that doesn't necessarily mean that they've got to get some money from the VA for research on spinal cord injury paralysis, most of it from the Neurological Institute, some from some voluntary organizations—I'm sorry, that's not the way to do it, in my judgment.

Dr. ROWLAND. I suppose that it's true in every situation in life, that one who has experienced an adversity is much closer to whatever caused that adversity and approaches it in a much more honest and open manner.

Thank you very much for being here this morning.

Mr. EDGAR. Mrs. Johnson.

Mrs. JOHNSON. Thank you very much.

Dr. Sabin, as one whose children were infants during the time your work came to fruition, I join Dr. Rowland in commending you on the promise that you brought to children throughout the world, and the comfort that you brought to parents, and the contribution that you have made to mankind in your life.

I have two brief questions. First of all, you have talked about the disadvantages of multiple agencies distributing money for the purpose of research in a single area. Of the agencies currently in-

volved in distributing money for spinal-cord investigations, which agency do you think is best prepared to be the lead agency?

Dr. SABIN. I think the National Institute of Neurological and Communicative Disorders and Stroke has the largest amount of funds and the major responsibility for dealing with these neurological disorders. It is not the Institute. It is the people who serve on the advisory board, and I'm not sure that—Look, I have been with the NIH too many years, and it doesn't necessarily mean that the advisory boards are always the best, because we are dealing here with a basic principle of problem-oriented research and general research.

I think that if the VA supplies the salaries of the good investigators that it has now, and the facilities and the laboratories which they have—when I look through here [pointing to a book], these VA investigators are already good enough to compete for funds with investigators in other academic institutions. I cannot see why those working in VA facilities should be in a dirrerent category from other investigatiors. But I also think the research has to be coordinated. I think most of the time that duplication in things like this should be done only when it's necessary.

We have had occasions when some way-out reports were made about regeneration and so on, and then the work was repeated by others and the results were not reproducible.

Mrs. JOHNSON. Dr. Sabin, my experience with Government certainly supports the wisdom of your advice.

Let me ask you, finally, how valuable do you think the nuclear magnetometer radiation, the NMR technology, is going to be in the early treatment and care of spinal-cord-injury paralysis, and can you give me any indication as to how you see this technology in comparison, for example, to the CAT scanner?

Dr. SABIN. To the extent that nuclear magnetic resonance may supply different information about the condition of the spinal cord shortly after injury, it could be very, very helpful, more so perhaps than the CAT scanner.

Mrs. JOHNSON. Is there any setting in——

Dr. SABIN. I think there are people here who will be able to answer it much better than I.

Mrs. JOHNSON. Thank you very much. It has been really an honor to have you here today.

Mr. EDGAR. Mrs. Johnson, I might mention that we had a little workshop in this room on Tuesday on nuclear magnetic resonance machines, and both within the VA and outside the VA there are a number of imaging devices that are being used. Our St. Louis facility, for example, I think has an NMR machine. It is just now being approved by the Food and Drug Administration as a clinical tool as opposed to a research tool. So while many people have been imaged by an NMR machine or something in that line of imaging, it is not in full use, even in the private sector, to the extent that it probably will be. It is more a research tool.

Mr. Bilirakis.

Mr. BILIRAKIS. Thank you, Mr. Chairman. I apologize to you, sir, and to Dr. Sabin for my tardy appearance.

I first became acquainted with Dr. Sabin from a direct standpoint when he was a witness at one of our Select Committee on

Aging hearings, and you were just as powerful a witness at that time.

Dr. SABIN. Yes, 3 months ago.

Mr. BILIRAKIS. It is nice to see you again today.

I have no questions, sir. I would merely ask permission to place an opening statement in the record. Thank you.

[The statement of Mr. Bilirakis follows:]

OPENING STATEMENT OF HON. MICHAEL BILIRAKIS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF FLORIDA

I join you in welcoming our distinguished witnesses to this hearing on VA medical research programs. It is a privilege to have this opportunity to hear from such highly respected experts in the medical research community.

The work you and others are carrying out today—as researchers into neurological disorders, spinal cord injury and regeneration, Alzheimer's disease, schizophrenia and other debilitating disorders—continues the VA's pioneering tradition in medical research. That tradition has produced numerous important advances, great and small, in medical science and improved the lives of countless people, both veterans and non-veterans alike. I am confident that the VA's research programs will continue to make notable contributions to the practice of medicine.

I have a particular interest in one area which will be briefly discussed this morning and again, in more detail, at the subcommittee's June 13 hearing on geriatric and aging research. I am speaking about Alzheimer's disease, a tragic, degenerative illness which robs its elderly victims of memory and reason and of the chance to enjoy their golden years in health and dignity. The Select Committee on Aging, on which I serve, will be holding a hearing on Alzheimer's in my district on May 19. The area of Florida I represent is the fastest growing area of older Americans in the nation and similarly, has one of the country's fastest growing veteran populations. Alzheimer's disease, as well as the other serious health problems which are the subject of VA research, are, therefore, of critical interest to my constitutents and to me. I greatly look forward to your testimony and want to thank you for taking the time to discuss your work with us.

Mr. EDGAR. Dr. Sabin, let me ask you just two specific questions. From your experience with your own medical illness and paralysis, what observations do you make about health care in relationship to your own experience?

Dr. SABIN. I will have to get it off the top of my head as it comes. First, nursing to the paralyzed person is absolutely of the first and greatest importance. Without proper nursing, a paralyzed person is helpless. I would be put to bed at night and I couldn't move. I was like a crucified person. I would just lie there, you see. So good nursing, compassionate nursing—and it takes a lot of compassion in order to put up with some of the things you have to do for a paralyzed person—is very important.

Another thing that comes to my mind, and it certainly isn't everything, is that there was a phase just before I became completely paralyzed and actually was dead on August 30, 1983, when my heart stopped, my respiration stopped, and I was unconscious and had to be resuscitated, just before then I had the most excruciating pain I ever had in my life. I don't think that medical care at the present time is sufficiently cognizant—at least the people that get the responsibility of taking care of excruciating pain—to stop pain. From Hippocrates we have the first dictum, "First of all, do not do any harm." Every doctor, every student remembers that. The second one, I would say, should be: "Remember, you have got to relieve pain to the maximum possible effect."

When I was sick with excruciating pain and yelled for relief, to get a brushoff from the doctor on duty, and nurses who couldn't do

anything by themselves, it was a very awful experence—I can't forgive them. This went on until I died. So that all the concern they had about preventing trouble with my respiration did not prevent the audio-respiratory arrest. They could have done other things but they didn't—and I died. And then a private assistant nurse who was in the room raised the alarm. If it was up to the people at the nursing station, I don't know, too much time might have elapsed to permit resuscitation. Maybe my brain is still afffected now because I may have been without oxygen too long. Maybe my colleagues here may think, he's been without oxygen so long that his brain is not working too well now. Maybe so. I haven't noticed it.

But the point is, if this poor assistant nurse didn't yell out: "Dr. Sabin is dead," and if the resuscitation team had not come up as quickly as they did, I would have been dead. So there are all sorts of aspects.

The other aspect that I think is so very important is the work that is being done by the Veterans' Administration on rehabilitation. The rehabilitation that I had from the Public Health Service physiotherapist at the National Institutes of Health, was just simply out of this world. When I couldn't sit up and I couldn't do anything, his patience and fortitude motivated me throughout. There are many things that a paralyzed person can be trained to do—and you have evidence of that in the Veterans' Administration, with so many centers. That is all important.

Let us strive by research and development to get all the new knowledge that we may be able to get to prevent SCT paralysis, and perhaps ultimately to restore function, but let us not overlook the urgently needed care—never mind "cure, not care," the way I read some of this. I say care, care, and let the research go on until we have new knowledge. But until we have that new knowledge, care is all the more important. I feel that very strongly after all I have been through.

Mr. EDGAR. Some of us had a sitdown dinner a few weeks ago with Norman Cousins, who went through a similar kind of experience, and who is now teaching at UCLA, and felt as though he had not only died but was designated as terminally ill on several different occasions. He talked about the emotional attitude that was necessary.

But he also talked about nurses, and he also made a comment which I would like to ask your reflection on; that is, the training of doctors may be very good and competent in terms of dealing with specific illnesses, or at least our state-of-the-art knowledge of those illnesses, but may lack some strong components in terms of the caring for the patient, in terms of the overall environment of that patient, the total mental and physical health of that patient, including the family and support system. He pointed to some research that indicated that when they told patients they were terminally ill with cancer or their prognosis was very limited, that the patients went downhill almost immediately because of the way in which they were being told what was wrong with them. There wasn't the sensitivity to that individual.

I wonder if you might reflect just for a moment on that issue.

Dr. SABIN. It is being said very, very generally now that medicine has become 90 percent or more knowledge and less than 10 percent

compassion. Whereas, before we had all that knowledge, there was more compassion.

Well, in order to be able to exercise compassion, you need time. Time is what the present system of medical care somehow or other does not permit. Therefore, I think that the good points that you have already mentioned, and to which I subscribe the need for, greater compassionate relationship with the patient, requires time.

In one way the physician can't do everything. Certain things have to be allotted to different people, some doctors and some paramedicals, but then when it comes time to put the whole thing together, the physican has got to have the time in the hospital setting to really get into the patient's feelings and into his head. We have to create time, and that can be done only by certain reorganization—not having more doctors or more nurses. It is the way of doing things that needs reorganization.

Mr. EDGAR. It's kind of a balance between high tech and high touch, being able to not only technologically help someone, but also to be able to touch someone.

Dr. SABIN. Yes; high tech may only make it impossible to give proper medical care. It has its limitations. Nuclear magnetic resonance about which we talked, it's a terribly expensive thing. I happen to have been involved with this some years ago, before it was developed as a possible medical tool, and if you're going to do nuclear magnetic resonance for every damned thing that a doctor could do simply by putting his ear or stethoscope to the chest or doing other things, then the high tech will make it impossible to give proper care. So high tech alone is wonderful when you need it in a way that no other procedure will supply. But the way to do it—You're going to get every hospital now go out and try to get nuclear magnetic resonance and you're going to throw away the millions of dollars you have already invested in CAT scans. There's room for CAT scans and room for nuclear magnetic resonance. The way to do things is very important, and it has to do with research as with medical care.

Mr. EDGAR. Mr. Penny, do you have any questions of Dr. Sabin?

Mr. PENNY. Mr. Chairman, no questions, but just a word of appreciation to Dr. Sabin for all his work on polio. My father suffered from polio during the epidemic back in the late forties and the first few years of the fifties, and though he came through it, a lot of people didn't. I want to thank you for your efforts that have been so successful in eliminating that threat to health in our society.

Dr. SABIN. Thank you very much, but I would like for you to remember, as most people don't remember, that in the world that is inhabited by at least half of the total world population, paralytic polio is still a most serious disease which has not been eliminated and which could be eliminated only by proper procedures that are now used in only a few countries. I hope that more countries will do it.

You see, it also shows that merely having knowledge is not enough. You have got to have a way of using that knowledge. And in research and development you have got to develop knowledge with a view as to how it's going to be used, never mind if you can get regeneration in a newt or a goldfish.

Mr. PENNY. Dr. Sabin, I appreciate that clarification. As you may have noted, I said in our society. It is important, as you have stated, to remember that though we have eliminated the threat here in America, it does exist throughout the world and there is still work to be done.

Mr. EDGAR. On behalf of all of us, I want to thank you for taking the time to be here and to stimulate our discussion this morning. I really applaud your efforts and appreciate your taking the time to come, particularly given the traumatic year that you have been through. Thank you very much.

Dr. SABIN. Thank you very, very much.

Mr. EDGAR. Our next witness will be Mr. Jack Powell, executive director of the Paralyzed Veterans of America. It is a pleasure to have you here this morning. The full text of your statement will be made a part of the record.

Would you introduce the person who is with you today, and I would ask that you proceed.

STATEMENT OF R. JACK POWELL, EXECUTIVE DIRECTOR, PARALYZED VETERANS OF AMERICA; ACCOMPANIED BY LYNN PHILLIPS, NATIONAL RESEARCH DIRECTOR, PARALYZED VETERANS OF AMERICA

Mr. POWELL. Thank you, Mr. Chairman. It is always a pleasure to be here.

I am accompanied today by Miss Lynn Phillips, who is PVA's Research Director.

I have to make an aside, too. Being from PVA, I am used to appearing at the end of an agenda rather than second on an agenda, but I am not used to—whether I appear at the end of an agenda or second on the agenda—following such eloquent testimony as preceded me this morning.

I was going to start out by talking about the fact that once every hour in this country somebody is confronted with a spinal cord injury that will result in the rest of their life being spent in a wheelchair. However, there is no real sense in doing that because Dr. Sabin certainly brought that home more clearly than I could.

Research efforts have made significant advances in neurological research during recent years. It is because of the great importance that neurological research holds for the members of the Paralyzed Veterans of America and thousands of other disabled citizens in this country, and the promise of such research, that we are especially grateful for this hearing today. We hope that the efforts of the Veterans' Administration and other research entities will receive greater public and Government attention through such hearings. Further, we hope that increased resources and emphasis will be directed toward this vital and necessary field of research, which includes spinal cord regeneration.

One of the mandates of PVA's congressional charter is to promote research. Therefore, we are very proud of our organization's contributions to the growing field of spinal cord research that currently is expanding in this country, and we take our responsibilities in this area very seriously.

PVA's Spinal Cord Research Foundation was created in 1976 to formalize PVA's research efforts. In the past 9 years, our foundation has awarded more than $2.5 million to spinal cord research, including regeneration research.

In the field of spinal cord regeneration research, PVA would like to commend the Veterans' Administration for its efforts in this important area. Since 1980, the VA has operated an Office of Regeneration Research at the VAMC in Portland, OR with Dr. Frederick Seil as Director. This office serves as the VA's central coordinating point for regeneration research information.

There are two major accomplishments of the VA's regeneration research program to which I would like to draw particular attention. First, that office has initiated a series of symposia which gathers together experts in fields related to regeneration, both within and outside the VA. These symposia have provided neuroscientists with the opportunity to discuss face to face the work they are doing and to compare their findings. In doing so, they challenge one another's research techniques and, most importantly, explore new ideas for future research. That is how progress occurs in a complex field such as this, and the VA has begun to take a leadership role in providing this type of exchange opportunity.

A second accomplishment of the VA's Office of Regeneration Research has been the development of a quarterly publication, the "Regeneration Research Newsletter." To our knowledge, it is the only regular newsletter on the topic of regeneration research, and thus fills a major void in the area of information dissemination. We would encourage the VA to continue publication of this newsletter and to expand it so that it becomes a primary resource for people involved in regeneration.

From our contact with researchers in spinal cord research, it is clear that some of the most highly recognized leaders in this area are associated with VA facilities. Dr. Stephen Waxman, for example, who is testifying here today, is a nationally recognized figure in his field, and he also serves as a member of PVA's own scientific advisory board.

The disappointing fact remains, though, that so many other investigators in central nervous system regeneration are not affiliated with the VA. From our conversations with researchers, it appears that one of the major disincentives to working in the VA is the low level of research support available. In order to build a good laboratory within the VA, it is often necessary to utilize clinical funding as a supplement.

VA clinical personnel are well aware of the direct benefit research has for their patients. In the past they therefore have been quite willing to provide support for research from their clinical budgets. However, as demands on clinical services have increased, that sharing of resources has become less prevalent. This, in effect, represents a cutback in research.

The relationship between good patient care and good research has been stated many times, but it bears repeating. The way to attract qualified, inquisitive physicians and other staff to a VA hospital is to provide them with research opportunities. As an aside from our testimony, PVA has testified before this committee and other committees on numerous occasions on the impact that re-

search provides to the Veterans' Administration in attracting the type of physicians that provide good medical care to the patients in the VA system. So it is not research alone that is the single benefit of the VA's involvement in research. In turn, their research efforts can benefit both VA and non-VA patients in improved diagnostic and treatment techniques.

The field of regeneration research is one of the most compelling areas for the VA to be involved in, since the treatment of spinal cord injury was pioneered by VA physicians in the post-World War II era. It would be most fitting for the VA to lead the effort to cure this presently incurable condition.

I had just a few other brief comments, but I would like to change that and just comment on a couple of thoughts that Dr. Sabin's testimony brought to my mind.

Certainly we have testified before on the importance of nursing to catastrophically disabled patients, and we were certainly glad, in response to the chairman's question, that Dr. Sabin was given the opportunity to talk about the tremendous burden that is placed on nursing personnel caring for catastrophically disabled people. It is a different place than any other place in the hospital.

Second was the importance of rehabilitation, which also Dr. Sabin talked about. Whether we argue that the implantation of computer chips be rehabilitation or research, ambulation smells as sweet under any name.

Last, but not least—and it is difficult to disagree with someone with the reputation and the prestige of Dr. Sabin—PVA must question the appropriateness of single agency funding for research. In our efforts over many years, we have dealt with the National Institute of Neurological and Communicative Disorders and Stroke, and we have dealt with other agencies of the National Institutes of Health. We have dealt with a broad-based number of different governmental agencies.

We do, however, share Dr. Sabin's concern about the coordination of the efforts that take place. We would point out that the Office of Regeneration Research in the VA we think is a very significant step forward. As a very small organization involved in research, we have been confronted constantly with the questions of duplicative research and that type of thing, and sharing information is almost as important as the information that is developed directly out of research, so that you don't have duplication.

I would like to point out here again that under the Carter administration there was a task force established in the White House to coordinate spinal cord research. That task force died with the change of administrations, and we think it was a very inappropriate and untimely death. In an area of this importance, that cost this country many billions of dollars. It would seem that at the very least there should be a coordination of efforts between various agencies. But we don't believe in putting all the eggs in one basket, of one agency.

That completes my testimony, Mr. Chairman.

[The statement of Mr. Powell appears at p. 51.]

Mr. EDGAR. Thank you very much.

You were articulate, I think, in one point in your testimony by pointing out the fact that it is not just research that we're talking

about within the VA, the fact that research may be the magnet that draws the competent professionals to the VA to also provide the competent care, but there is that very important balance that we have to maintain. I appreciate your underscoring that.

Could you describe a little more carefully the Office of Research Coordination that died in this administration? Where was it located within the White House?

Mr. POWELL. It was specifically located under the Office of Science and Technology Policy, Dr. Denis Prager in the Office of Science and Technology Policy in the White House. He was made chairman of that task force.

The concept was that it would bring together representatives of the various agencies of Government who are participating in or providing funding for spinal cord and spinal cord-related research, to coordinate these efforts in an attempt to cut back on the duplication that sometimes takes place, No. 1, and No. 2, as well as do some of the distribution of work force effort, and No. 3, to bring in some of the private organizations.

I know the reason PVA was involved is that oftentimes, before a researcher can successfully go to NINCDS or NIH to receive funding, they need preliminary grant funds in order to prove enough of the thesis of their argument, in order to pass the selection and the review boards. So, it brought in private sector organizations like PVA, who oftentimes provide this money, and attempted to make a coordination between the private sector, the halls of academia, and the Government agencies, to coordinate this effort. We thought it was an extremely appropriate approach.

Mr. EDGAR. Your office or staff may want to make contact with a Florida Congressman by the name of Buddy MacKay. Last night he took on the responsibility of becoming chairman of a task force of the Clearinghouse on the Future, to try to do a better job of coordinating research and research dollars within the Federal Government. They are not certain yet how they're going to pursue that, but a number of futurists and academics, as well as professionals in the General Accounting Office and the Library of Congress and Office of Technology Assessment, volunteered to work with him on trying to look at ways in which the Congress of the United States could do a better job of understanding and coordinating some of the research. You might just want to talk with his office and his staff about your interest there.

You mentioned on page 2 of your statement that PVA has awarded $2.5 million for spinal cord injury research. I know that your brochure summarizes some of your efforts. PVA is to be commended for the projects that you're involved in.

Just for our record, could you briefly tell us about some of the efforts—and divide your answer into two parts—one, your general overall efforts in general research, and the other thing that Dr. Sabin talked about, your problem-oriented, specific-targeted research efforts. Could you list out for the record a couple of the things you're doing with that effort?

Mr. POWELL. I would be happy to do it and take the credit for it, but I have the person who does the work day in and day out with me, so I would like to, with your indulgence, ask Ms. Phillips to address that.

Mr. EDGAR. Ms. Phillips.

Ms. PHILLIPS. Thank you. I appreciate having the opportunity to describe some of what PVA is doing with respect to research.

First of all, it is easy to answer what we're doing in terms of general research, because we don't do general research. We do specific problem-oriented research. PVA funds research in areas relating to any research area concerning spinal cord injury. We basically consider these in three areas: basic research, which is regeneration-oriented research; applied medical research, which applies to better medical care for spinal cord injured persons; and then technological research, which looks into better devices, functional electrical stimulation, to encourage a new ambulation and so forth.

Within the area of regeneration research, we have funded research in the past in virtually all of the areas currently being examined. For example, one area that is being looked at is implanting fetal tissue into nerves within the central nervous system and the peripheral nervous system. We have funded a Dr. Howard Normis out at the University of Colorado in this area.

Another area in regeneration research that we have looked at is applying electrical fields to try to stimulate nerves to regrow themselves. But I think what we want to emphasize is that there is a strong need for smaller funding sources like PVA, private funding sources like PVA, like the American Paralysis Association and so forth, to provide the seed funding so that people can qualify later on for larger funding grants from NIH or from the Veterans' Administration.

I would like to reiterate what Mr. Powell said. It is oftentimes necessary to have many different kinds of funding sources available, because each agency has its own basic premises upon which they are building, and we can provide the seed money, NIH can look at the overall area of research, but the Veterans' Administration needs to be concerned about the specific needs of the veteran it serves. It has been a pioneer in the area of spinal cord injury and I would really like to see it be a pioneer in the area of curing this problem as well.

Mr. EDGAR. Mr. Bilirakis.

Mr. BILIRAKIS. I have no questions, Mr. Chairman.

Mr. EDGAR. Dr. Rowland.

Dr. ROWLAND. Thank you, Mr. Chairman.

How much duplication of effort do you think now exists in research, in the Government and outside of the Government, and with respect to that, do you think that pride of discovery or pride of development causes some duplication of research, and if so, how can we deal with that?

Mr. POWELL. I think there are several questions about duplication. Dr. Sabin talked about the state-of-the-art at a given moment. It is not necessarily, therefore, true that a research project done on a specific question 10 years ago, and then repeated today, is automatically duplication. The state-of-the-art, the ability to examine—we talk about NMR and all these types of things—the state-of-the-art and the ability to examine a given question may have expanded greatly to actually get through to an answer during that intervening period of time. However, I do believe that, while I would hesitate to put a number on it, that certainly duplication of effort, the

rediscovery of previously answered questions, is an ongoing concern that anybody involved from the standpoint of awarding funding to research has.

There are several major problems that all come together, I think, on this aspect. One is that I think there is an innate resistance by scientists themselves to share with other scientists what they are doing and where they're at for fear that, one, they're going to be beaten to the punch, so to speak; two, that they may lose their funding source—let's face it. You know, we talk about NINCDS, we talk about NJH. One heck of a lot of the research done in this country is done by NIH. So that means everybody is coming back to this one pyramid. The guy that gets there first with the proposal stands the best chance of getting funded. So nobody wants to talk. So, because of that, you have duplication.

We recently visited a facility in Florida, in which—I would call it in the biological sciences area. We were informed by scientists there of certain research that they were doing that we had been informed of on a trip to Stanford University, which was taking place there 2 years before. While I know for a fact that the scientists involved happened to know each other, it was obvious they were not talking to each other about specifically what each one was doing, although they may have been doing it in generalities. It is an ongoing concern, what can be done to resolve that problem.

For example, PVA reviews every project proposal that it gets against proposals that have been submitted to NIH. We also compare proposals that we have received on an ongoing data file with other spinal cord injury organizations who fund research. It has got to require an effort between those people who grant the money to screen and to assure that—there are unscupulous people out there; there are lazy people out there. I know in my involvement with PVA since I have been the executive director of their Research Foundation, we have seen for sure 100 proposals submitted on which we know the work has already been done and the answer is already there.

Now, it is either ignorance on the scientists' part, or laziness on the scientists' part, that causes that kind of thing to occur. But it is our obligation, and it is the obligation of anybody who is going to write the check, to do that kind of screening.

Dr. ROWLAND. I certainly think you have shed some light on the question that I posed, about the loss of funding if the information that an individual has developed becomes known to others and the pride that an individual has in what they have developed over a period of time, and to share that with someone else who may take the ball and the individual who did the initial basic research is lost. It is very much of a consideration that we need to address. I don't know that there is any way that can be resolved and I will be interested in hearing what other people have to say about that.

Thank you for your testimony.

Mr. EDGAR. I just have one final question.

In your review of your proposals, do you have a board of scientists and professionals who help you to review what you say yes or no to?

Mr. POWELL. We go through three cuts, Mr. Chairman. We start out with a scientific advisory board that is made up of seven people

who are—I would call them more or less generalists. While they each come from a specific area having a relationship to SCI care, medicine and research, they have their own specialized fields, but they have a general knowledge as well of what has taken place in the area of research. They start out with the first cut.

Then we have over 150 scientists divided by specific category from around the country, the best in each of their various fields. Any proposal that makes it past our scientific advisory board process is sent out to at least three experts in the same field that that proposal is written in for a peer review. Those experts fill out peer review forms on that proposal and grade it on the basis of the science in the question that is being asked, the appropriateness of the budget and the capability of the researchers to carry out that. That all then comes back in, although they are considered by our board of trustees who come up to a final decision on which proposals are funded and which are not.

Mr. EDGAR. Thank you very much for detailing that for us and for testifying today. I appreciate it.

Mr. POWELL. Thank you, Mr. Chairman.

Mr. EDGAR. I would like now to call up a panel of VA witnesses, beginning with the Deputy Chief Medical Director, Dr. Gronvall, Dr. Boren, Dr. Davis, Dr. Waxman, Dr. Bernstein, and Dr. Seil.

Before you begin, I would like to thank Dr. Boren and his staff for all of the assistance that you have given the staff of this committee in putting together today's hearing and the two additional hearings that we are holding. I appreciate your efforts in that regard.

Let me call first for the statement of Dr. John A. Gronvall, who is the Deputy Chief Medical Director of the Department of Medicine and Surgery. It is a pleasure to have you here today. We were hoping to have Dr. Custis here and I called him this week and urged him to come, even though he was retiring. But I can understand his reasons for not being here. We appreciate your coming in his stead.

STATEMENTS OF JOHN A. GRONVALL, M.D., DEPUTY CHIEF MEDICAL DIRECTOR, DEPARTMENT OF MEDICINE AND SURGERY, VETERANS' ADMINISTRATION; HOLLIS G. BOREN, M.D., ASSISTANT CHIEF MEDICAL DIRECTOR, RESEARCH AND DEVELOPMENT, DEPARTMENT OF MEDICINE AND SURGERY; KENNETH L. DAVIS, M.D., CHIEF, PSYCHIATRY SERVICE, VAMC, BRONX, NY; STEPHEN G. WAXMAN, M.D., PH.D., CHIEF, NEUROLOGY SERVICE, VAMC, PALO ALTO, CA; JERALD J. BERNSTEIN, M.D., CHIEF, LABORATORY OF CENTRAL NERVOUS SYSTEM INJURY AND REGENERATION, VAMC, WASHINGTON, DC; AND FREDRICK J. SEIL, M.D., DIRECTOR, OFFICE OF REGENERATION RESEARCH PROGRAMS, VETERANS' ADMINISTRATION

STATEMENT OF DR. JOHN A. GRONVALL

Dr. GRONVALL. Thank you very much, Mr. Chairman. You can tell that I bring a medical problem to the table today.

Mr. EDGAR. Without objection, your full statement will be made a part of the record. [Laughter.]

Dr. GRONVALL. Let me just try to make a very brief comment. We very much appreciate the kind comments you have made about Dr. Custis. We will carry those back to him.

I appreciate your willingness to incorporate my statement. I should just say that we appreciate very much the opportunity that you are giving us to present to you the work that is going on in the Veterans' Administration.

I think that what I should try to do is save my voice in case there are questions.

[The statement of Dr. Gronvall appears at p. 56.]

Mr. EDGAR. We appreciate your coming, even under the adverse conditions of your voice. I think this is your first appearance before our committee in your new capacity, is that right?

Dr. GRONVALL. Yes, it is.

Mr. EDGAR. We appreciate your coming and look forward to working with you in the future on common issues.

I know this will be referenced later on, but I would like to make note and hope those in the audience will take a copy of the medical advances on the VA contribution to health care, the special research document. Dr. Boren may speak to that in a few minutes. But I just want to make note that it's available for people to look at and to understand what some of the specifics are in the research area.

Dr. GRONVALL. Mr. Chairman, if I might, I think I could say a few sentences about this publication.

Mr. EDGAR. That would be helpful.

Dr. GRONVALL. We are very pleased that this hearing coincides with the availability of this report. The report actually was suggested to us by people outside the VA, particularly those in the service organizations, who felt we did not have at the present time an adequate way of displaying and describing the research work going on throughout the VA. So with their stimulus, we developed this report.

We do it not to really "toot our own horn" but to tell an honest story of accomplishment and to display the ways in which research, together with education and patient care, can continue to provide for our veterans' care which is second to none.

Thank you.

Mr. EDGAR. Thank you very much.

Dr. Boren, we are pleased to have you here. Again, thank you for your assistance in these hearings. We look forward to hearing your statement. The full text of your statement will also be made a part of the record and you may proceed as you see fit.

STATEMENT OF DR. HOLLIS G BOREN

Dr. BOREN. Thank you, Mr. Chairman. It has been a pleasure, indeed, working with you and the members of your committee, in preparing for these research hearings.

If we think today of three words—Alzheimer's disease, schizophrenia, and spinal cord injury—we will be thinking diseases that are not killing diseases but which are devastating for the patients and their families. There can be no other three conditions as devastating as these. I would also say there would, therefore, be no re-

search more important than in these areas, no matter how difficult this research is.

I view my role here today as largely introducing our expert witnesses in the area of Alzheimer's disease, which accounts for some 27,000 diagnoses per year, and more frighteningly, will increase a threefold amount by the year 2000, since it is an age-related disease. We have Dr. Ken Davis from the Bronx Hospital who will discuss alzheimer's disease.

When we think of schizophrenia, it accounts for 1 out of 6 patients in our hospitals. In our psychiatric wards, it accounts for 84 percent of all of our patients. This is a major problem for the VA. It led to the VA establishing two schizophrenia biologic research centers, one at the Bronx and one at Palo Alto. Dr. Davis is the director of the Bronx Schizophrenia Biologic Research Center and his second topic will be on schizophrenia.

On spinal cord injury, Dr. Sabin has already given you the numbers of the VA workload and I will not repeat these. We have with us this morning Dr. Steve Waxman from Palo Alto, who will set the stage for spinal cord regeneration and talk about neuronal growth.

Dr. Fritz Seil, on my far left, will talk about the overall place where research is going, and in between, Dr. Jerry Bernstein will talk about fetal transplants in spinal cord injuries.

That concludes my summary, Mr. Chairman.

[The statement of Dr. Boren appears at p. 60.]

Mr. EDGAR. Thank you very much.

We would like all of you to summarize your statements, as you see fit. We are going to hold off the questions until the end. It may be a little confusing in doing that, but since you have selected the four areas to focus on, we think we can focus back in those four areas after we have heard all of the testimony.

STATEMENT OF DR. KENNETH L. DAVIS

Dr. DAVIS. I am Ken Davis, the chief of psychiatry at the Bronx VA. I am affiliated with the Mount Sinai School of Medicine in New York.

As Dr. Boren mentioned, I am going to discuss both schizophrenia and Alzheimer's disease, two health problems affecting millions of Americans, and I hope to conclude with the implications of this research to the clinical care of veterans in our hospitals. Let me begin with Alzheimer's disease.

A series of truly extraordinary studies that were conducted in the United Kingdom between 1976 and 1977, and since widely replicated around the world, have told us something very important about Alzheimer's disease. That is, we now know one very important kind of brain cell that is dying in patients with Alzheimer's disease. That brain cell makes a certain chemical called acetylcholine. There are very few brain cells that make acetylcholine, but it is apparent that these cells are dying in the brains of patients with this disease.

Now, on the basis of that deficit, which we call a cholinergic deficit, or a deficit in acetylcholine, my colleagues and I have proposed to attempt to reverse that pharmacologically with drugs, particu-

larly with a drug that is called physostigmine. We have been conducting this research with funding from the National Institutes of Health and the Veterans' Administration. I would be pleased later to discuss the nature of overlapping or duplicate funding, which seems to be an important topic here today.

What we have found in the use of this drug physostigmine is summarized in a figure that is on page 4 of my statement.

First let me tell you first a little something about physostigmine. This drug takes what acetylcholine is being made by patients with Alzheimer's disease, which we already know is deficient, and it keeps that acetylcholine around a little longer.

Clearly, some patients, patients who are so disabled, so severely affected by this disease that they are not making any acetylcholine, or only negligible amounts, would not be helped by this drug. But others, who have modest levels, might be benefitted. What you see in that figure is, in fact, exactly what I have told you. That is to say, those patients who seem to have the most acetylcholine available, though still an abnormal amount, are those people who are helped the most by physostigmine, and those people with very little are helped quite minimally, if at all.

How many people are helped? Well, it looks like in our sample about one-third of our Alzheimer's patients have a clinically meaningful response to physostigmine. This work has been replicated in other centers where they have been as fortunate as to find two-thirds of the patients with some meaningful clinical change.

But what do I mean by that? Well, we are still talking about people who were demented, and after therapy with this drug, still remained quite demented. This is a very modest step.

But we are pleased, as scientists, about what this means. Of course, for the patient the effects are not as impressive as they would like, nor as uniform as we would desire. But they point us, we think, in important directions for future research. In fact, a proposal that is presently before the VA Cooperative Study Section is to see if we can't identify that subpopulation of Alzheimer's patients who may be modestly benefitted by physostigmine treatment.

Of course, regardless of the outcome of the review of that application, we recognize that physostigmine is by no means an ultimate treatment for Alzheimer's disease. Rather, we have to turn in some new directions.

Research in many other areas has been helped by animal models. Because of some truly brilliant work that was conducted at Johns Hopkins, it has become possible for the first time to conceptualize putting a lesion in the brains of rats and in monkeys that can produce the same deficit in acetylcholine that occurs in Alzheimer's disease. By producing that deficit, we have at least taken one first step in developing an animal model. Of course, it is only a first step because in many ways these brains don't at all resemble the brains of Alzheimer's patients, but that model may help us develop drugs more rapidly.

Some work that we are doing, again with funding from both the National Institutes of Health and the VA, is transplanting cells from embryonic tissue into animals who have those lesions, to see

whether we can reverse the abnormal deficit of these, if you will, "demented" animals by more novel techniques.

Now, another real problem in Alzheimer's disease, both clinical and research, is the identification of the disease, the diagnosis of the disease. You would think that is a rather straightforward problem but, unfortunately, it is not. We can only make a definitive diagnosis of Alzheimer's disease when we have the confirmation by brain tissue, autopsy or biopsy verification. Obviously, autopsy verification is too late to help us, and biopsies are rarely done in the United States. Therefore, we have been looking for some clinical test that may help us diagnose this disease, perhaps even early on.

You can see on page 7 of my prepared testimony some squiggles and wiggles that were taken from an electrical recording from the scalp of normal people. What happens, as you see on the left-hand panel, are little bumps that occur that can be recorded after normal people hear a sequence of the same tone. When a novel tone is superimposed on all those same tones, we see in the right-hand panel some new bumps. Those late bumps that are labeled P3 and N2 seem to us to be very important in Alzheimer's disease. Because as the table on the following page illustrates, we have, by using those late components of what we call evoked potential paradigms, been able to differentiate Alzheimer's patients from normal controls. Again, that may not seem very impressive because, to paraphrase some of the people that work in my laboratory, some of our patients, even the butcher can tell who are demented. So what does it mean—that our expensive equipment can tell that as well?

Well, what it means is we have taken the first step toward developing a technique that may help us differentiate not only Alzheimer's disease from normal people, which is easy, but perhaps Alzheimer's disease from other kinds of dementia, which is hard. That is work that is in progress and we hope to see the results of in the next few years. But I would like to point out it was funded by the innovative VA initiative in aging that began last year. That work is being conducted by a colleague in my laboratory.

On page 9 you see another potential way that we may be able to diagnose Alzheimer's disease. What we are looking at here, in collaboration with an endocrinologist in our laboratory, is nocturnal or nighttime cortisol levels. To our surprise, there seems to be substantial differences between patients with Alzheimer's disease and normal people in the amount of cortisol they put out at night. Alzheimer's patients seem to put out a lot more. We wonder whether this, too, may not help us differentiate Alzheimer's from other kinds of dementia, and that work is again in progress.

Let me now turn to schizophrenia research. As Dr. Boren pointed out, schizophrenia is a major, if not the major, problem in the VA. One out of six beds are filled with schizophrenic patients. Because of the cost to our population, to the veterans population, and the VA, in 1981 the VA launched a new initiative to establish two schizophrenia biological research centers after a national competition. I am the Director of the one at the Bronx.

Our schizophrenia biological research center has been interested in a chemical, another kind of neurotransmitter, in this case not acetylcholine that I mentioned earlier with Alzheimer's disease, but a neurotransmitter called dopamine. There are many symptoms of

schizophrenia, and many effects of drugs that we use in schizophrenia, that can be explained by their effects on this chemical dopamine.

I am going to be taking you through a series of studies in which we have measured the major breakdown product of dopamine, or what happens to dopamine in the brain after it is used. That breakdown product we refer to as HVA or homovanillic acid. You can take it to mean a "footprint" for dopamine.

An important question that we have been looking at is whether there is any difference between schizophrenics when they are ill and schizophrenics when they become well. We know it's a chronic disease, but it's a disease characterized by remission and relapse. Can we find the biological changes that underlie the symptom changes as patients move from remission to illness? That has been a major thrust of our work.

You see on page 10 of my testimony the first step in that direction. What we are looking at here is, in spinal fluid, levels of HVA, that breakdown product of dopamine. What we see is that, indeed, schizophrenics who are relapsed differ from schizophrenics who are remitted in this important product. We have also been looking, as you see on page 12, at a hormone, a growth hormone, which is influenced by dopamine levels in the brain. Here, too, we see important differences between schizophrenics who are ill and schizophrenics who are well, as well as between any schizophrenic and normal people.

Now, this is by no means to say that we know what causes schizophrenia—far from it. But we hope that it may help us conceptualize other directions to pursue in the next few years.

Short of this idealistic goal of identifying the cause of schizophrenia, let me talk about some more immediately clinically relevant issues. As some of you may be aware, by having watched about 2 months ago the CBS report on the "Nightly News" about tardive dyskinesia, this is a syndrome characterized by involuntary movements of the mouth and face, that happen to schizophrenic and other psychotic people who have been receiving antipsychotic drugs. In my hospital, among my schizophrenics, about 10 to 20 percent of all people have mild forms of this unfortunate iatrogenic or doctor-induced disease. We induce it, of course, not by choice but because it is the only treatment we presently have, antipsychotic drugs, that do it. We are very concerned about this and we are looking for ways to understand it and to treat it.

You can see on page 13 a small step that we have taken to at least understand a little more about what is behind tardive dyskinesia. Here we are looking again at HVA, that major breakdown product of dopamine, and what we are asking is, how is it changed by a drug that we give. We find that in patients with tardive dyskinesia, in patients without tardive dyskinesia, the levels of HVA after we give that drug go down in different degrees. We think that is a hint about what may be happening in tardive dyskinesia and we are going to build on that, we hope, to develop perhaps some preventive measures.

Now, another major problem that those of you who have visited our hospitals are probably well aware of, is treatment-resistant schizophrenics. An unfortunately large number of schizophrenics in

our system are, in fact, in our system because they don't get well. Present treatments just aren't adequate. We don't understand what is the biological basis of their disease.

It would be, of course, a great advantage if we had some blood test that could help us differentiate who, in fact, will respond to antipsychotic drugs from who won't. At present, we don't have such a treatment. A number of us are looking for that. And I will just show you some work in progress that appears on page 14.

Basically, what this figure demonstrates is that if we measure the major breakdown product of dopamine, again HVA, in the blood before we start treatment, it looks like that we can tell who, after 4 weeks of treatment, will still be very ill. It looks like those people with the highest levels of plasma HVA before treatment stay ill the longest.

Well, as to future research in schizophrenia, there are a number of new technologies, which we have heard a little bit about today, such as nuclear magnetic resonance, PET scanning, positron emission tomography. I would suggest perhaps that molecular genetics may in the future offer us new insights into this condition. But I think it is important—and I hope it doesn't appear too self-serving for me to emphasize—that I would think that whatever technologies, new or old, help us understand schizophrenia in the next 20 or 25 years, that the vision that the Veterans' Administration demonstrated in establishing schizophrenia biological research centers will, I believe, contribute to the understanding of the biology of schizophrenia simply because these centers remain the only Government-funded program outside the NIMH that are solely dedicated to research in this disabling condition.

Let me conclude by putting on my other hat for a second and discuss the impact of medical research on the clinical care of veterans.

As both the chief of psychiatry in my department, and the investigator on much of the work that I discussed today, I think I have a unique perspective on this problem. My views can best be seen by reviewing the history of psychiatric care in my facility over the last 5 years.

When we recruited from Palo Alto, Stanford University, the Bronx VA and Mount Sinai, we found a psychiatry service that really was in disarray. It is with some trepidation that I want to tell you that our accreditation was not what we would have liked in that psychiatry service. Our ability to recruit residents was far from adequate. The ability to retain staff was not what any of us would have liked. Patient satisfaction surveys showed general dissatisfaction by the population we were serving, and our occupancy rate for a Veterans' Administration hospital in psychiatry service was extremely low.

In the last 4 years we have completely reversed this situation. The psychiatry service at our hospital now has the highest joint commission accreditation. Our occupancy rate exceeds 90 percent. Patient satisfaction surveys show a high degree of satisfaction with our program. Our residency program is not only completely filled; it has grown. All our staff physician lines are filled, and they are not only filled with good physicians, but I think with some of the best trained physicians in the country, people from Harvard, Yale,

Stanford, and graduates of the NIMH programs. As a result—and this is really critical—I believe our patients receive care today that is better than is given in most other psychiatric facilities anywhere in the country—new treatments, better assessment, and more detailed diagnosis. It was only through a high quality research program that we could make that possible.

Clinical investigation has been the impetus to the high quality care that we believe we now give. So if I can leave you with one impression today, it is that the funds the VA appropriates in its research program produces benefits that are many times as great as are funds that are actually allocated. Simply put, I could not retain my staff without the VA's research program. Rarely does a program spend less and obtain more, at least from my perspective, than does this program. In the case of my hospital, it has been the difference between providing patient care that I believe will be the quality of care, or I hope will be the quality of care, in most psychiatric facilities by the end of this century, instead of psychiatric care that none of us would find satisfactory.

That concludes my statement. I will be pleased to answer any questions that you or the members of the committee may have.

[The statement of Dr. Davis appears at p. 65.]

Mr. EDGAR. Dr. Boren, would you like to introduce your next witness?

Dr. BOREN. I would like to go on with Dr. Steve Waxman, who is the Chief of Neurology Service, VA Medical Center in Palo Alto, CA.

STATEMENT OF STEPHEN G. WAXMAN

Dr. WAXMAN. Thank you, and thank you for inviting me to speak here today.

Mr. EDGAR. Dr. Waxman, your full text will be made a part of the record. We would ask you to proceed and hope you might be able to summarize as well.

Dr. WAXMAN. OK. What I would like to do today is briefly talk about research on neurological diseases and mechanisms of recovery from neurological insults within the Veterans' Administration.

This is a very exciting time for those of us who work in this area. There has been remarkable progress in this area over the past several years. At the same time we really do face some very significant challenges in the future. You have been hearing and you will hear a lot about the word "regeneration." I like to view that word in its broadest sense as connoting reorganization at the tissue level, at the cellular level, or at the molecular level, as long as it results in recovery of function. We do occasionally see a patient with stroke who recovers from the paralysis. We desperately want to understand why, so that we can develop therapies which would promote recovery in still other patients. We see patients with multiple sclerosis who experience remissions, functional recovery, and again, we desperately want to understand why. We have made some very significant progress in that area.

So what I would like to do is just briefly talk about some of the progress that has been made in this area, some of the prospects for further progress, and some of the problems.

Now, as you know, the VA has a very long standing and deep interest in this problem. In terms of spinal cord injury, there are at least—and this is a very conservative estimate—100,000 patients, many of them young, who are paralyzed from spinal cord injury at this time in the United States alone. I think it is fair to say that our medical system has made very, very remarkable strides in the care of these patients. But at the same time they have been focused primarily on symptomatic care, treatment of complications such as decubiti, bedsores, urinary tract infections, et cetera. I think it is fair to say that at the moment we still do not have any effective curative therapy which is going to reverse the paralysis that these patients have. These patients are still in their wheelchairs and we, therefore, need to do better.

Now, at the same time it has become very clear that nerve cells exhibit an inherent capability to reorganize following various disease insults. We call this plasticity. We are optimistic that we may be able to harness this plasticity within the clinical domain in terms of treatment modalities. So that is the problem.

What I would like to do is briefly walk you through some of the diagrams in my written statement to show you where we are, or at least give you a flavor of that.[1]

Figure 1 is a diagram of a nerve cell, a neuron. It is a very complex structure, but in outline the areas that are labeled I and II are the receptive pole where the neuron receives electrical impulses from other nerve cells. What concerns us today is the area labeled III. This is the nerve fiber or the axon. This is the area where the nerve cell sends messages to other nerve cells, tiny electrical messages, which are very crucial for communication between nerve cells. Nerve fibers of this sort descend from the brain in the spinal cord and, ascend from lower levels to the brain in the spinal cord.

Now, we know that after transection of an axon, a nerve fiber, in peripheral nerves, that nerve fiber will often regenerate and in some cases will reach its proper target and establish a functional connection. But in contrast to that, nerve fibers do not regenerate very effectively at all within the brain or the spinal cord. That's the problem.

Mr. EDGAR. Would you say that one more time?

Dr. WAXMAN. Yes. Currently, in mammals and certainly in man, there is very little evidence for significant regeneration under most circumstances of nerve fibers following injury in the brain and spinal cord. An important distinction, is that the peripheral nerve fibers will regenerate very briskly.

One important model disease for us is multiple sclerosis. Figure 2 here shows a section through the brain of a patient with multiple sclerosis. Multiple sclerosis is important to me, as a neurologist and as a scientist, for two reasons: One is that we have in this country over 200,000 patients with multiple sclerosis, so in terms of its medical and psycho-social toll, it is an important disease in its own right. But the other point is that MS, multiple slerosis, may serve as a very instructive model disease, because it is one of the few diseases of the human central nervous system in which we see func-

[1] The diagrams referred to appear in the prepared statement of Dr. Waxman begin on p. 83.

tional recovery in the face of apparently fixed structural abnormalities.

This diagram shows the lesions that we see in multiple sclerosis. The areas that are white are areas in which nerve cells have lost their surrounding coating, and despite that, we do see recovery in this setting due to very subtle reorganization of the affected nerve cells. So it is a very important disease for us to understand, and we have begun to understand at the cellular level what is going on in this disease.

Now, back to the nerve cell. What do we know about the nerve cell? In figure 3 we can actually see the electrical impulses by which nerve cells communicate. This particular recording of this tiny electrical signal comes from the spinal cord. We can record these tiny signals that are a fraction of a volt. We can do this from normal cells; we can do it from damaged nerve cells as they regenerate or as they don't regenerate. And we can test the effects of various putative therapies on this electrical communication.

We know, for example, that these electrical signals are produced by tiny molecular batteries. We call the sodium channels, but they're tiny batteries within the nerve cell membrane. On figure 4 is shown something that couldn't have been illustrated 5 years ago, a picture through the electron microscope where we can actually visualize these sodium channels, these molecular batteries, within the nerve cell membrane.

But there are still problems. How are they produced? What is the gene for these batteries? Once they're produced, how do they get put in the cell membrane and what holds them there? These are big problems for us.

Figure 5 shows a set of recording from a regenerating nerve cell. We can do all of these things in regenerating nerve cells, and we can actually watch them reestablish their function and begin to communicate with each other once again. Figure 5 also shows several recording before and after treatment to this nerve cell with a drug which causes the channels to produce more electrical current. This is an example of a type of compound which is being screened as a candidate for symptomatic therapy in the demyelinating diseases like multiple sclerosis and in cord injury. So I think we are beginning to develop some very effective technologies to study nerve cells, how they grow, how they respond to injury.

Finally, I would like to just briefly talk about lower systems which do show a brisk recovery following damage to brain or spinal cord. Figure 6 shows the spinal cord of a fish that we're studying in our laboratory. It's called Sternarchus, the black ghost knife fish. The work on this particular system is quantitatively a very small part of our program, approximately 15 percent of our effort, but we think it is a very important part because we are beginning to learn about how nerve cells respond to injury in this species.

In figure 6 you can see a normal spinal cord, and in figure 7 a regenerated spinal cord, in which new neurons are produced following injury. Then in the final figure you can see that one can actually isolate neurons, grow them in the laboratory in tiny plastic dishes and ask questions about how neurons grow and how they differentiate after injury.

Now, despite the progress that I have outlined, there are many more and pressing questions that stay in front of us. As an example, what are the mechanisms by which nerve cells grow and establish their complex geometry? What turns on neuronal growth, and equally important, because we don't want to end up with a tumor, what turns off neuronal growth? What guides a growing nerve cell to its correct target and, once there, how does it establish the proper connection? Then, finally, how can we encourage all of these processes after injury to the nervous system?

I personally don't feel that it is realistic to expect that we are going to regenerate complete new spinal cords on patients after total spinal cord injury. I do think that it is entirely realistic to expect that we can encourage conduction through damaged nerve fibers and that we may be able to encourage regeneration of some small subpopulation of nerve fibers in a damaged spinal cord.

I can tell you that this is a very highly motivated group of patients, and that if we can accomplish that, these patients will put those residual fibers to very good use.

That concludes my statement and I will be happy to answer your questions.

[The statement of Dr. Waxman apears at p. —.]

Mr. EDGAR. Thank you very much. I want to also thank you for your explanation when we visited your site in Palo Alto and we appreciated the briefing we received there. I appreciate Dr. Davis coming and sharing some of his testimony as well.

We are going to have to recess for about 10 minutes to go over and make a recorded vote on the House floor. This is part of the thing that we get elected and paid for. So we will be glad to come back in 10 minutes.

This hearing will stand in recess.

[Whereupon, the subcommittee was in recess.]

Mr. EDGAR. The subcommittee will come to order.

Dr. Boren, we will proceed with the two remaining witnesses before we reach our questions.

Dr. BOREN. Yes, sir. I would like now to introduce Dr. Jerald J. Bernstein, who is Chief of the Laboratory of Central Nervous System Injury and Regeneration, at the Washington VA Hospital.

STATEMENT OF DR. JERALD J. BERNSTEIN

Dr. BERNSTEIN. Thank you.

Mr. Chairman, ladies and gentlemen. In 1980 I was recruited into this program by the Veterans' Administration to establish a laboratory which would undertake the development of a basic research program to identify areas of research for an eventual cure in para- and quadriplegia. Basic science at this moment is the only approach to find a cure for this disease that affects so many people and is so costly to our society.

Spinal cord injury that results in para- or quadriplegia is a disconnection of the spinal cord from the brain. The body below the injury has no sensation or controlled muscle movement. In addition, there is pain of unknown origin, the muscles below the injury waste away, and there are many other problems. The nerve fibers that connect the spinal cord and brain after the injury are either

mechanically damaged or cease to transfer information across the area of injury. To date, research has not led to a solution of the problem of the inability of the damaged nerve cells to regrow across the site of injury.

Humans and other animals have their total complement of nerve cells and nerve fiber processes in early infancy. After that time, no new nerve cells or nerve fiber processes as we know are produced. Therefore, we have established the goal in our laboratory of establishing a method of supplying new, growing, and active nerve cells to a damaged adult spinal cord of a paraplegic.

We have initiated experiments in the first nervous system spinal cord transplants in an animal model. The objectives of these experiments are to see if the transplant would live, if we can really put in new nerve cells, if we can get regrowth of new nerve fibers from these transplants, and if new nerve connections can be made to make new nerve circuits from the transplant to the spinal cord and back again.

Now, in your blue folder, if you don't mind taking out the illustrations in the back of it—and I don't want to cause any anxiety, but there will be a short exam after this neuro-anatomy lecture. [Laughter.]

Mr. EDGAR. Do you grade on the "curve"? [Laughter.]

Dr. BERNSTEIN. For you, Mr. Chairman, they will only be true or false. [Laughter.]

Mr. EDGAR. I appreciate that. Will there be someone there available to help read the questions. [Laughter.]

Dr. BERNSTEIN. The first diagram is a representation of the normal spinal cord. This miraculous structure contains nerve fibers on the outside of the spinal cord which transfer information from the brain to the body through the spinal cord and from the body through the spinal cord back to the brain.

This information includes sensations from the body, most of which you are unaware of until you think of them. Are my socks tight? Did I wear that pair of shoes with the strap that always rubs my toe? Is my leg in that position I always place it in when I sit at my desk, which shortens my muscles, so when I stand up I limp?

It is inherent in these questions that there is not only information of body sensation and position transferred from your brain, but also information is coming from your spinal cord up to your brain. In this case just mentioned about your leg muscles, for example, how did your leg muscles shorten? It is by means of a brain-transmitted message. This information is passed in the nerve fibers in the outer spinal cord, as seen in the diagram, and the information is gathered in the body and sent by the nerve fibers into the top aspects of the spinal cord. The muscle movement information comes out of the bottom, so you can see body sensation versus muscle movement. So the diagram now in front of you represents the spinal cord at the upper illustration at the top of the body and the lower illustration in the bottom of the body. The butterfly structure in the middle is the nerve cell circuits that are in the spinal cord.

If we turn to the next diagram on page 2, just by turning it up, you see the consequences of a spinal cord injury which results in paraplegia. In this injury we have a disconnection of the spinal

cord, so the body is disconnected from the brain and the brain is disconnected from the body. This would come from severe whiplash, in which your car is going zero miles an hour and you are struck from behind by a truck doing 60 miles an hour, and you violently snap your head back. You just bruise the spinal cord. It will disconnect. Even though the structure is there, it will disconnect functionally.

So we are now presently faced with the fact that you have a loss of sensation and a loss of movement below that site of injury. As we mentioned earlier, you cannot, nor can any mammal, produce new nerve cells after infancy. What can we do to replace the lost nerve cells and nerve fibers and now make a new circuit?

Our experimental attack on the problem is to provide a source of new nerve cells which we will study for their survival, their growth, their ability to produce new nerve cells, and new connections. What we are doing now, we are taking the spinal cord and the brain of a developing rat as the model and placing it into the spinal cord of an adult animal. It must be remembered that this is the only source of new nerve cells that any mammal can have that we put there at the moment.

If you will look on page 3, you will see how we placed the transplant. We actually dissect out a piece of this brain, and as we do this, we place the transplant into the lesion with a needle and just drop it in. I can tell you now that the developing tissue survives, if you will look at illustration four, the research goal for paraplegics. We have kept it alive for as long as 6 months in other animals, and that is when we terminated the experiment. I could say it grows by adding new nerve cells which no adult could do before, and I could say it retains its normal ability to make new nerve cells, because it is still developing. We have accomplished this and we are on the forefront of the first spinal cord transplant. Even for me, this sounds like science fiction. We are now studying the spinal cord transplants in animals, as was done in earlier stages of liver and heart transplants, which we all accept now as routine.

The next figure, figure 4, demonstrates our expectations in this research. I would like to stress that these experiments are still in the developmental stage and it would be impardonable of me to give false hope to the many victims of paraplegia. However, with these caveats, I would like to look at the expectations that we have.

The transplant has now grown to fill the injury site, which it does, by the way, and there are new nerve cells and nerve fibers that grow from the transplant out into the spinal cord and into the brain, and then from the brain itself down into the transplant. There is a bridge that has been made, and this is our expectation and our hope, that the nerve fibers will grow across this bridge and then re-establish the conductivity between the upper cord and lower cord and the brain.

Now, I would like you please to turn to the next page and show you what these really look like. If we take a look at the overlay, you can see now the spinal cord of a rat. If you look on the outside, the dark purple structures on the outside are those nerve fibers which are connecting the brain up and down, as I told you, and in the middle there should be an island of purple nerve fibers. In the

center you see the butterfly, that sort of magenta color. That contains nerve cells.

Now, all of the area that is cross-hatched should all have the purple-only nerve fiber area in it. If you pick up the overlay, you will see a small, round, magenta colored area that looks integrated with the other magenta colored area. That small area is the transplant. It is now integrated with the spinal cord. It may have cross talk with the spinal cord. In this case, this has lived 30 days and it is the first case that we have seen of a spinal cord transplant in our laboratory which has integrated.

We must now determine if the adult spinal cord and the transplant will form the interconnections between them, and we must determine if there is the return of function. Most of all, we want to know if these implants will reverse the tragedy of paraplegia. The work must continue or we'll never know the answer.

That concludes my statement, Mr. Chairman. Thank you very much.

[The statement of Dr. Bernstein appears at p. 92.]

Dr. BOREN. Last is Dr. Fredrick Seil, the Director of the National Office of Regeneration Research, at the VA Medical Center in Portland, OR.

STATEMENT OF FREDRICK SEIL

Dr. SEIL. You heard already about this office to some degree from Mr. Powell and I would like to just add a few comments to that.

The office was established in 1981 and is located in Portland. The purview of this office is regeneration research, basic regeneration research in the broad sense. It includes all tissues—for example, bones, limbs, muscles, liver, kidney, nervous system, of which the spinal cord is a part.

You have heard something about our newsletter, and this is an example of our most recent issue. This newsletter is mailed to we interested scientists all over the world who have an interest in regeneration research.

Mr. EDGAR. Would you make a copy of that available to us?

Dr. SEIL. Yes, gladly.

Mr. EDGAR. I would like to put that in the file of this hearing.

[The newsletter appears at p. 110.]

Dr. SEIL. We have also been active in organizing symposia as another means of increasing communication among scientists who work in this area. One of these symposia, one held in 1982, resulted in the publication of a book, which Dr. Sabin showed you a copy of. Consistent with the mission of the office, this book was broadly based and covered various aspects of regeneration research. There was one section on spinal cord research. There were also sections on regeneration of muscles, limbs, gut and liver.

One of the interesting byproducts of having a symposium where there were scientists from these various areas of regeneration was that we could learn from each other and that there are, indeed, some common problems in all aspects of regeneration. There are some basic issues that go across various kinds of tissue, and this kind of interaction was very valuable, indeed.

I would like to go on now and tell you about some other kinds of research that is going on in the VA, in addition to what you have heard from Doctors Waxman and Bernstein, that relate to nervous system regeneration. One example has to do with improving and promoting peripheral nerve regeneration by means of inserting plastic tubes between cut ends of a peripheral nerve. When you cut a peripheral nerve, normally the ends retract from each other. They move a distance away. Two VA-funded researchers, Dr. Betty Uzman in Memphis and Dr. Richard Sidman in Boston, have been working with putting plastic tubes in these gaps to promote the growth of a bridge between the two cut ends. I have here some samples of the kind of tubing that Dr. Uzman uses with her experiments with mice, these plastic tubes. I should point out that in figure 1 of the statement you will find a diagram of how this kind of experiment is constructed.

Dr. Sidman has extended this work to the optic nerve, which is the nerve from the eye to the brain, and has found, indeed, that there is a similar regeneration, a similar growth of optic nerve into these tubes.

The ultimate hope is that if this kind of technique works with optic nerve and peripheral nerve, perhaps it will work also with a more complex structure such as the spinal cord. So by learning these things in steps, we may gain the kind of knowledge that will allow these experiments to be performed in a more complex system.

Another area of great interest is the study of growth factors. About 30 years ago, Dr. Rita Levi-Montalcini in St. Louis described one of these factors as the nerve growth factor, and this factor was found to promote survival of nerve cells and to promote development and growth of nerve fibers. In figure 2 of the statement you will see a picture of some sensory neurons that were grown with and without this nerve growth factor protein. You notice in the bottom figure the tremendous outgrowth of fibers that are present when grown in the presence of this nerve growth protein.

In subsequent research it has been found that there are other factors. The pattern seems to be developing that there are factors specific for many different kinds of nerve cells. The importance of these factors may be that they may be present during development of the nervous system.

As you have already heard, higher animals are already born with all the nerve cells they're going to have, and they are very unsuccessful at regenerating structures like spinal cord. Some lower animals, such as the Sternarchus that Dr. Waxman was talking about, are, indeed, successful, and they also happen to be able to produce nerve cells throughout their adult lives.

It is also possible that some of these growth factors that are present during development may disappear when they are no longer needed. The difference between an animal that can regenerate versus one that can't may be, in part, due to the presence of growth factors. So, it becomes very important to identify these substances, because in order to induce regeneration in higher animals, it is conceivable that we may have to supply them artificially. This is a very rapidly expanding field and there are a number of labora-

tories, both within and outside the VA system, that are devoted to this problem.

A final example is one that comes from my own laboratory, in which we are able to grow nerve cells under glass, so to speak—that is, in glass chambers, such as the one I have here, which didn't entirely survive the trip from Oregon. But we can, with these simple culture systems, put together small fragments of nervous system tissue and watch them develop in a living state under a microscope. What we can do is put together different levels and see how they interact and learn the rules by which they make connections with each other.

We can also take, for example, a group of nerve cells—there is a specific defined population of nerve cells that are highly interconnected. We can give this group of nerve cells a certain type of drug that destroys only one of the several types of cells that are there, and then we can look at this and see what new connections are made to compensate for the missing elements. Then we can take this one step further and ask, now that we've got this kind of reorganization that is compensatory, if we now introduce these missing elements back into the system, will there be a second round of organization and will it go back toward the normal. The answer is yes, indeed, it does. So again, this gives us some idea of what kinds of priorities there are for making connections within the nervous system. As in any other walk of life, the right connections have to be made in order for the system to function properly. So this is again a very active area of regeneration that is getting and deserving a lot of attention.

If you ask me where I think regeneration research is going, I think that you're going to see a lot more of the kinds of experiments that Dr. Waxman, Dr. Bernstein, and I have described. I think you are going to see remarkable developments in the area of transplantation of the nervous system. I think you are also going to see a lot more studies that will define and understand the role of nerve growth factors, and I think also you're going to see a persistent and steady progress in understanding the development of the nervous system which is critical to understanding regeneration.

In terms of what has been accomplished in the past, it is actually remarkable. We're in an era of considerable growth and expansion in this area. Only about 15 or 20 years ago it was thought that the central nervous system couldn't regenerate at all. That has been disproved. There have been a number of experiments that show, even in higher mammals, at least some partial regeneration under given circumstances. So this has been cause for a great deal of hope and certainly has given us a lot of impetus to continue with these kinds of study and look for the factors by which we can promote regeneration.

Now, we are certainly a long way in terms of looking at basic research and applying it practically to man. But I think this is a young field, it is making a lot of progress, it is making very rapid progress, and I think it will not be too long before we can look forward to using the fruits of research, indeed, to benefit mankind.

Thank you, Mr. Chairman.

[The statement of Dr. Seil appears at p. 103.]

Mr. EDGAR. Thank you very much. I want to thank all of you for your statements.

I am going to yield to my two colleagues before I ask my 32,602 questions. Dr. Rowland.

Dr. ROWLAND. Thank you very much, Mr. Chairman. I welcome my colleagues to this committee. I feel very comfortable with your testimony this morning.

Dr. Davis, I want to ask something about the cortisol and growth hormone levels that you talked about in schizophrenia. We have been having some hearings and investigation and oversight in the Public Works Committee, and we have been talking about air traffic controllers and the fact that air traffic controllers have elevated cortisol and growth hormone levels. So this brings up a question as to whether or not these are elevated because of what took place, or were they, in fact, causing what took place.

Would you care to comment on that?

Dr. DAVIS. Thank you for such an erudite question. Obviously, you are at home with this work.

Traditionally, endocrinologists would believe that the concomitant elevation of growth hormone, cortisol, especially with prolactin, is a stress response. I have never seen first hand the air traffic controller information, and I don't know whether they just had cortisols up or cortisols, both hormones and prolactins, and that was a reflection of stress.

The question as to whether what we're seeing in our schizophrenics and Alzheimer's patients is stress or not, I don't believe it is stress—for the following reason. In schizophrenia, we don't find elevations in prolactin or cortisol, but only these erratic, unaccountable bursts of growth hormone activity. They come when we would least expect them. They don't come in response to pharmacological probe. It seems simply like a disregulated system.

In collaboration with the Salk Institute, we are now looking at cerebrospinal fluid to see whether a compound that has just been identified, a growth hormone releasing factor, may be aberrant in those patients. We are very excited about following up on why we're seeing this disregulated growth hormone function.

In our Alzheimer's patients, again we know, because we have looked simultaneously at growth hormone prolactin, that these are not up in Alzheimer's disease. Rather, we see a relatively specific deficit in cortisol. We have a number of hypotheses on why it is up, and it is only modestly up. We think it may reflect a noradrenergic deficit as well as acetylcholine deficit. We think it may reflect a faulty feedback because of cells that are dying in the brains of the patients with Alzheimer's disease. Again, in collaboration with a number of endocrinologists, both in and outside my institution, were trying to answer the question of what's happening in the feedback loop in Alzheimer's disease that may tell us something more about the disease itself.

Dr. ROWLAND. I guess we're going to have to wait a little longer before we will be able to get an answer to that question.

Dr. Bernstein, I am ready for your test now, and if you wouldn't mind throwing in a couple of questions like the two neuron reflex arc and things you didn't talk about here. I know we were unable

to set the curve in school, but I might have a reasonable opportunity of setting the curve here.

Let me ask you about how far along you are with the research and regeneration, and perhaps Dr. Seil could talk about that also. I really am enthused and intrigued by what is taking place here.

Dr. BERNSTEIN. The transplantation in brain and spinal cord research is going ahead at such a rapid, rapid pace, it is incredible. In Sweden, there are four patients with Parkinson's disease who have had their brains implanted with cells from their own body, chromafin cells from the adrenal gland, which produced norepinephrine, which they need put into their ventricles of their brains to see if it would help them. The results are equivocal, but it is the first sign of transplants in humans.

The pace of the research is amazing. In animal research, in brain transplants, we now know there is some behavioral recovery which is coming from the transplants, and if they find it in the brain, we could hope then to find it in the spinal cord. There are connections being made in the brain using the transplant as bridges, which is information that we needed in the spinal cord. We have yet to accomplish this in the spinal cord, but it does occur in the brain.

There are learning deficits that are induced in animals by making a certain lesion in their brain. You make a hole in their brain such that the animal can't do a particular behavior. You give them the transplant, they can do the behavior. Transplant research in animals is going ahead so rapidly. We know there are connections being made; the new cells live; the new cells have conductivity, and where they have survived, they seem to have some effect in ameliorating or lessening the course of the disease or the deficits. So it looks very hopeful now and research is moving ahead more rapidly.

The problem is, to tell you the truth, that as I sit here, I know someone else is publishing. I would rather be in the lab.

Dr. ROWLAND. Do you have any comment?

Dr. SEIL. I might just add one of the other benefits in the transplants. Because one uses embryonic tissue, they may also be a source of the growth factors that may be necessary, and this may be one other reason why we get some benefit from this procedure.

Dr. ROWLAND. One other question, Mr. Chairman, and then I will yield. And I would direct this to any of you who may want to answer it. This was a point that I brought up earlier.

Do you have any particular feeling about the pride of development, of discovery, on the part of researchers insofar as duplication of effort is concerned?

Dr. DAVIS. Are you referring to duplication of funding?

Dr. ROWLAND. No, sir. I am talking about—well, funding and effort, both.

Dr. DAVIS. Well, in my field, duplication of effort is absolutely essential to replication. We have to have a number of laboratories working on the same problems with different perspectives in order to confirm that, in fact, what a single lab is doing is correct.

As far as funding sources, you may be aware that the process of review, particularly in these times of relatively scarce resources for researchers, is such, and the community of researchers so small in any given field, that usually your colleagues are on the review

committees that review grants and are quite aware of other sources of funding. In fact, grants stipulate that you specify where your other sources of funding are coming from. There can be no duplication. No study section will let pass a duplication of funding.

Dr. ROWLAND. I suppose you might say, then, if duplication of effort is necessary to check what other people are doing, and this research is dependent on funding, then duplication of funding would almost have to follow as being necessary.

Dr. DAVIS. Duplication of funding to other researchers, but not within the same lab. For instance, when I receive funds from the VA and the NIH, those are two different things.

Dr. ROWLAND. Thank you very much.

Thank you, Mr. Chairman.

Mr. EDGAR. Mr. Bilirakis?

Mr. BILIRAKIS. Thank you, Mr. Chairman.

I tell the folks back home of the fantastic learning experience I am having here, I guess maybe learning is not quite the right word—because I'm not sure we learn that much—but we gain much knowledge. I commend Doctors Gronvall and Boren particularly for having developed this panel and sharing all of this knowledge with us.

I am going to go into some of the technical questions, questions which certainly Dr. Rowland is more capable of asking. One thought comes to mind: Is it possible for lower animals to get Alzheimer's disease and to have schizophrenia and whatnot? I would also like to concentrate on an area that is of grave importance. Dr. Rowland mentioned it, and we talked about it somewhat in running over to the Capitol to vote a few minutes ago.

You know, there is only so much money to go around, and yet research and experimentation is so very, very definitely needed. I know that what Dr. Davis says is true, that there has to be maybe some duplication of effort in order to have it be true experimentation and true research.

Mr. Powell alluded to the coordinating function that took place at the White House under the previous administration, which no longer exists. I know that all of you, of course, work for the Veterans' Administration. But I wonder if we could touch—and God knows, I think all of Congress ought to concentrate more on this—and that is, do we have adequate coordinating functions? Do we overduplicate the efforts? Do we overduplicate the funding? Yesterday one committee devoted the entire day to the National Science Foundation and their research. I think we all agree that there is much good that comes out of that. But probably a heck of a lot of no good too that comes out of it and perhaps a lot of waste. I know that any research function will probably result in some waste, and that some things may come out of it which really are not very constructive, at least at that particular time. But I would surely like to receive some recommendations, some comments from you all, in terms of this overall area.

Is there something that the Government, that Congress can do to maybe dig into possible overduplication and overfunding and whatnot? Can we improve the efficiency of research and the efficiency of experimentation in some way, so that more of it can take place,

because there just isn't enough funding? Is there an awful lot of duplication that takes place, and duplication of funding?

Well, question on comment. I would certainly like to hear from you on this.

Mr. Chairman, I am greatly concerned about it. I think it is part of our function up here to be concerned about all of these areas and to try to do the best we can about them.

Dr. GRONVALL. If my voice will hold up for a minute, let me make a general comment. Then I would like to ask Dr. Boren to comment.

I think you have touched on an area of highly valid concern, and I think there are a number of mechanisms that are continually being put in place, refined or changed, to try to maintain collaboration. We have very active and regular and formal interaction between the VA and the Public Health Service—my voice is about to disappear. Let me turn it over to Dr. Boren.

Dr. BOREN. Yes. I would like to add that within the last 2 months we had a meeting with the group from the Public Health Service and talked about, of all things, spinal cord injury. Murray Goldstein was there presenting his part of what they were doing, while we were presenting what we were doing.

Another example is with the aging area. We work very closely with the National Institute of Aging. The Director there, Ed Snyder, gets together with our people in research; we get together with theirs. We talk about common problems, common goals, what our projects are, where our overlaps are, what we're supporting and what they're supporting, and where we're going. I think there is a tremendous amount of coordination. It is not fully across the board and it could be improved.

Mr. BILIRAKIS. How does your answer go in terms of the total medical community, not just the Public Health Service and the VA, for instance.

Dr. BOREN. I think there is a great deal of overlap. There are a fairly limited number of scientists and they tend to serve on different review panels. For example, we have some 14 review boards. Those same people that sit on these boards there will also sit on NIH review boards, so they know what's going on. They serve as an informal network among investigators in the field. I do think we achieve a great deal of coordination through the informal networking as well as through seminars, symposia, workshops, newsletters and this sort of thing.

Mr. BILIRAKIS. Is there anything Congress can do to improve all of that, to result in a better utilization of the unfortunate limited funding that is available?

Dr. BOREN. I really have no answer to that.

Mr. BILIRAKIS. You're a medical research doctor and, of course, you're in this field because you are concerned about the area of research and experimentation and the great strides that can be, and obviously are, being made. Are you satisfied that those are taking place as quickly as they might be if we had a better coordinated effort?

Dr. BOREN. My own personal bias is, sir, that it is. I was sitting here trying to think, in answering your question, whether or not it would be the level of Dr. Keyworth at the White House, if that or-

ganization would get all the Federal research initiatives going on one track. We spend some $52 billion a year in the Federal budget. As a matter of fact, our VA budget does not show up on most documents and is rounded off, say, at $0.6 billion.

But whether one central office, such as under Dr. Keyworth, could function with a legislative mandate to accomplish more coordination, I think would depend upon the wisdom of Congress.

Mr. BILIRAKIS. I will yield, Mr. Chairman. I guess I'm not satisfied in terms of having received the answers I am looking for.

Mr. EDGAR. I thank the gentleman for yielding. My questioning is going to pick up on the same area.

Let me just get a few housekeeping chores out of the way. I would like to ask unanimous consent that the statement by Hon. Christopher H. Smith be inserted at this point.

[The statement follows:]

PREPARED STATEMENT OF HON. CHRISTOPHER H. SMITH, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NEW JERSEY

This morning's hearing is aimed at examining the VA's Research Program on Neurological Disorders, a field which could ultimately lead to the successful treatment of paralysis.

Mr. Chairman, the exciting advances in this field which have already been achieved by the VA researchers and other Federal agencies bring new hope to those veterans who have experienced spinal cord injury or dysfunction. I would like to personally applaud the accomplishments of the highly capable team of VA researchers in the area of neurological research, one of the most difficult research challenges facing medical science today.

Medical research at the VA is a natural outgrowth of the clincical tasks it assumes on a day to day basis and I am sure that today's testimony will futher illustrate this close connection.

Mr. Chairman, I look forward to the testimony of our witnesses this morning, and I congratulate you for scheduling this important hearing.

Thank you, Mr. Chairman.

Mr. EDGAR. Without objection, Mr. Hammerschmidt has some specific questions he would like to ask for the record, and I hope that you can respond to those.[1]

Let me pick up on this last set. I am enormously impressed, as I travel the country and as I listen to this morning's testimony, that in specific areas we are doing research, a large portion of that research is very helpful, very good for the future. But my question is very similar to Mr. Bilirakis', that we have a document—By the way, for those of you who haven't seen it yet, there is a very subtle thing on the document that I just picked up because of the lighting in here. There is a whole bunch of soldiers on the front cover that you can't see unless you look pretty closely. The staff was teasing back here, about old soldiers don't die; they just fade away. Well, there is a whole bunch of old soldlier fading away on the front of the document. It is the most subtle use of printing that I have seen in a long time. But here is a document, very well and very slickly done, that says what the VA is doing in research.

Let me ask you some specific test questions. What are the dollar amounts on an annual basis of VA research?

Dr. BOREN. This year we have $164 million.

Mr. EDGAR. A $164 million in fiscal year 1984 funding?

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[1]See p. 117.

Dr. BOREN. In fiscal year 1984, divided between our three services. In medical research we have $148 million, in rehabilitation research and development, $10.8, and in health services research and development, $5 million.

Mr. EDGAR. And next year's research budget will be in the neighborhood of what?

Dr. BOREN. It's $184 million.

Mr. EDGAR. And the increase is inflation, or is it specific new areas of research?

Dr. BOREN. About half of it is in uncontrollables. Of the $20 million and 155 FTE increase, almost 50 percent are uncontrollable increases.

Mr. EDGAR. Now, you have stated that a board oversees the decisions as to how research is made; is that correct?

Dr. BOREN. Yes, sir.

Mr. EDGAR. This is a board composed of what kinds of people?

Dr. BOREN. There are actually 14 boards, of different disciplines. They are almost all outside the VA and recognized for their national expertise. A research project which comes in from an individual investigator in the field must first go through the local research and development committee at the hospital of our medical center. They must look at it not only for its scientific value but to be sure that we have adequate protection of human subjects, and thjat animal welfare is given proper attention.

If approved, it will then be forwarded through the director of the hospital for merit review by one of our 14 boards. These boards will then look at it, and if it is approved, will assign a priority for funding. If funded, then the funding goes back to the local VA medical center for the execution of the research.

Mr. EDGAR. How often do you personally meet with the corresponding research directors in other Federal agencies?

Dr. BOREN. Almost on a monthly basis.

Mr. EDGAR. Do they ever say to you, "Dr. Boren, you're doing research in an area that we're doing research in, and we would like to coordinate an effort"?

Dr. BOREN. No, sir. Only in the areas that I mentioned a minute ago. In aging, there is a great deal of interest. This is an area where there have been common goals. Here is where we talk about how many Alzheimer's centers we should have, whether there should be teaching nursing homes, what is being done in the GRECC's and this sort of thing. This is where, I believe, the only area where we have questions of that nature.

Mr. EDGAR. Dr. Sabin mentioned in his testimony that the VA treated 18,000-plus patients for SCI from 1976 to 1982. To your knowledge, is there any other institution which provides clinical treatment to as many patients?

Dr. BOREN. Not to as many. I think we agreed on the numbers.

Mr. EDGAR. Let me ask another piece of that question. There was some discussion about a single agency doing the coordination; there was other discussion about that may not be a good idea because of the need for duplicative responses. But if a decision was made that the VA would be the lead agency in SCI research, could the VA handle that lead agency responsibility?

Dr. BOREN. I would frankly hope that we would not be the lead agency, for the reasons that have been discussed by Mr. Powell and so well by Dr. Davis. That is the very nature of the goal of VA research, that we have some 500 clinician investigators, of which research is the way of attracting them and keeping them for patient care. This is our primary mission. Research is not our primary mission. Since it is not, I do not think that we would be the appropriate lead agency.

Mr. EDGAR. Let me talk specifically about research. I think you have made the point about being the magnet to draw physicians and scientists to the VA because of your research component. But let me take a specific issue.

Dr. Davis mentioned his work, as well as the Palo Alto Center, in schizophrenia. The VA has committed a 5-year commitment to that research. What do you use as criteria in terms of extending that research for an additional 5 years, or terminating the research, and what kinds of assurances can you give to your research staff in the midst of their research that their efforts are going to be continued or discontinued?

Dr. BOREN. Would you like a one-word answer? Productivity. If the staffs of those two centers produce quality research results, which are in publications and referee journals, they will continue to be supported. If they do not, at the time they come up for merit review again, the chances are they would not pass that review. It has to do with how much bang for the buck you get, how much productivity that comes out of those programs, as to whether or not they are continued.

Mr. EDGAR. The real question is how do you measure productivity as well.

Dr. BOREN. The numbers of publications and refereed journals is the primary measure.

Mr. EDGAR. I guess I'm not smart enough to know why good writers get favored over good researchers.

Dr. BERNSTEIN. No. The rejection rate on articles in most journals is 70 to 80 percent.

Mr. EDGAR. So if you had a Ph.D./MD/scientist who also wrote for the Harvard Newsletter and took journalism classes, he might have a better chance, you know, if he's scientifically competent, but also as a better writer, than someone who——

Dr. BOREN. He has still got to be able to have expertise with the methods and be able to synthesize his results and put it in the general background of knowledge and come through with reasonable explanations that meet the criteria of his peers when they look at what he has written, not just how clever a writer he is. A very poor writer may be an excellent scientist.

Mr. EDGAR. Well, let's suppose you have met the productivity test on the study of schizophrenia and that you're on the verge of some real breakthroughs. How do you then go about telling your two centers that they're going to continue? Do you tell them they're going to continue on an annual basis? Do you come back and block that in in some way so that they know they have 4 years or 5 years to continue their research? How are you going to do that?

Dr. BOREN. Realistically, all we can tell anybody is they have 1-year funding, because that's all the money that we know we're going to have. So you say, depending upon the availability of funding, if you have made satisfactory progress, that you would hope you would continue this center for an additional 5 years.

The centers are a little bit different than individual merit review proposals. These only go for 3 years. The centers have a little bit longer funding because there's a bigger operation and we have more investment in them.

Mr. EDGAR. In the construction area of health care, we have a 5-year plan which is reviewed on an annual basis. Do you have such a thing for research?

Dr. BOREN. We do for research facilities but not for research programs.

Mr. EDGAR. Would it be of any value to have a strategic plan that could be reviewed by the Congress of the United States and by the scientists that you use on your panel, so that it was clear to you, as Director of Research, where it is you're trying to head over a 5-year period, what it is you're trying to accomplish, and to have some measure as to whether or not you have accomplished those goals?

Dr. BOREN. It would, indeed, be very valuable, but practically, what usually happens is that another priority area comes up and you have a fixed pot of funds. You take the funding out of the fixed pot for the current high priority area, so that it is not really possible, unless there are greatly expanded funds, to do long-range planning programatically.

Mr. EDGAR. I understand the answer to that question. I guess my thought would be that that's true even in the construction area, that there are priorities, there are earthquakes and there are major projects that, for political reasons and others, get slipped into the 5-year plan or slipped out of that 5-year plan if they're on the wrong side of the political decisions.

But wouldn't it be helpful to have a 5-, 10-, 15-year plan so that between now and the year 2000 you have some beginning ideas as to where you want to go?

Dr. BOREN. Certainly.

Mr. EDGAR. Let me ask another question.

Do you generate the questions, or are the questions generated by the researchers who are submitting proposals?

Dr. BOREN. By the researchers submitting proposals. We will, at times, issue requests for proposals, where there are things which come up which are a high priority area, such as spinal cord injury, in which we will issue a request and say we would like to have a letter of intent, and then the regular proposals, to go through merit review, in a given area. Other than that, in the nontargeted, nonpriority areas, they come entirely from individual investigators. They are usually oriented toward his or her discipline.

In our system we have the advantage that, again, investigators are seeing patients, and usually the driving force is what the patients' needs are. The questions that the investigators ask come from what they're seeing in the wards with their patients. This is the reason why we can have physicians such as we have here this morning, looking at schizophrenia and Alzheimer's disease and

spinal cord injuries, because they are seeing patients with these diseases and are treating them. So they have questions. They're intelligent, they're bright, and that's where the ideas come from by and large.

Mr. EDGAR. Suppose Dr. Davis or Dr. Waxman, or Dr. Bernstein, in the midst of their research, find a Nobel Prize winning idea, and come back to you and say, "Ah, ha, we have found this." Can you make an effort to set aside a block of funds for a period of years to study that particular area because you have cut it out as a cutting edge research area?

Dr. BOREN. We would not be able to do that immediately because we wouldn't have the funds. We might in subsequent years, if they come in with the proposal and justify it adequately, and we see in the next fiscal year what funds we could make available to set aside for a period of, say, 2 or 3 years, to see if, indeed, this is at the level you think it is.

Mr. EDGAR. Do you have a breakdown of the almost $200 million of expenditures for 1985 by category? You talked about the 13 disciplines. Do you have it by schizophrenia, spinal cord, that type of thing?

Dr. BOREN. Yes, sir.

Mr. EDGAR. How many different categories do you have of research?

Dr. BOREN. Oh, many, many, many, many. I can't give you the exact number.

Mr. EDGAR. Zillions, trillions, or——

Dr. BOREN. Hundreds.

Mr. EDGAR. I guess I'm asking whether it is a good idea to have hundreds, or whether it is a good idea to have——

Dr. BOREN [continuing]. Dozens.

Mr. EDGAR. Dozens. What would your response be to that?

Dr. BOREN. I think it is necessary to have hundreds, because if you consider what our cadre of reseachers are, some 5,000 people, they tend to have hundreds of ideas. These ideas tend to be infrastructures that addresses the patient care problems. If we could address the patient care problems by dozens of proposals, that would be fine. But we can't address the patient care needs by only dozens. It has to be within the hundreds frame.

Mr. EDGAR. Let me ask the people who are involved in research, I want you to put on your personal hats at this point and talk about your personal experience in terms of you're making a a contribution to the research area of the VA, in terms of how they do business, and you were going to talk to Members of Congress about how we might direct the VA to do their business. What are some of the kinds of things that you would hope for as a researcher that the higher echelon within the VA would respond to and want to do? Would it be longevity of funding cycles; would it be ability to raise staffing levels; would it be equipment needs within the system? What are the kinds of things, as a researcher studying in the field, that you think are critical in order to expand the volume of information in your areas?

Dr. DAVIS. Let me preface this, that I think it is important to keep in mind that, as I said in my testimony, without the program as it exists, there would be much poorer quality of care in the hos-

pital. Given that, I hope everyone realizes that any criticisms that I might offer are criticisms in a sense to fine-tune——

Mr. EDGAR. By the way, there is a "fail safe" clause in my question. No one will be taken out and disciplined severely, I hope.

Dr. DAVIS. What I'm trying to say is that I really am talking about a system that needs fine tuning rather than one that I am centrally criticizing, because the benefits to our hospital and to my program far outweigh any deficiencies.

I think, though, by some caveats and experiences that we have had over the last few years, we might be able to communicate to the committee some of the circumstances that can be problematic.

I entered into research, really, because of the VA career development award system. I applied for a VA career development award in 1976 and at that time, when I made application, my mentor led me to believe that there would probably be absolutely no difficulty with that application. In fact, there wasn't. However, other people from my hospital in other disciplines, who were also anticiating no difficulty, were for the first time really not funded. That was 1976, and perhaps that marks the watershed for when things began to get a little more difficult in the career development program.

When we moved in 1979, I attracted some very bright young people. One of them put in a career development award. Again we thought we would have little difficulty. He was at that time, it turned out, the only psychiatrist funded in that round. Despite the fact that most of the beds in the Veterans Administration are in neuropsychiatry, when I was funded there was only one other psychiatrist. When he was funded, he was the only psychiatrist funded.

The years late 1981, 1982, and early 1983 were partricularly bad for the career development program. An entire round was skipped. An outstanding scientist who initially received his award and was working at my hospital left because he was uncertain that when he reapplied he would be able to find funding to sustain his career in the Veterans Administration.

We then made application with another individual who for the first time in my experience with the program was approved and not funded. He left the VA.

I have another applicant who, because of his relationship with the schizophrenia center, has put in another application that, from what I heard, has been meritoriously reviewed, judged to be a good application, but once again approved and not funded. He was encouraged to resubmit, but, of course, there is no other funding for that individual for the next 6 months and he's going to be looking for another job.

Now, I bring this up because I think that the career development system is absolutely the way to initiate the best young people in our fields into the research process in the VA. Particularly for psychiatrists, if we're going to have a cadre of young people who are really going to be able to make substantial contributions, we have to do it through the career development system.

We were very, very pleased when the VA, in 1979, decided there would be schizophrenia centers. That followed a series of meetings and some real vision, since one out of six beds were filled by schizophrenic patients, that we needed to do a little more than we were

then doing. I am sure that if we divided the number of dollars that the VA spends by the number of patients afflicted by any disease, probably schizophrenia would be receiving less dollars per bed than any other disease that we are treating today. So we were particularly pleased when the schizophrenia research centers were funded.

However, our initial phase of funding coincided with the freeze in FTE, so even though our hospital had money, we couldn't spend it. I lost virtually an entire year from our research program because we couldn't bring people on.

Now we are unsure, as of December 1985, whether there will be funding for the schizophrenia center in 1986, but we have a core of some very good people establishing the kinds of very basic core laboratories and core assessments that make a lot of the research that I presented today possible. It would be good if we knew, if we had some long-term planning, to say for these people they don't have to start looking for jobs when the funding runs out. I am not sure in an annual budget kind of system we really know what's going to happen to those people come January 1, 1986.

Mr. EDGAR. So 5- and 10-year planning would be helpful, even knowing that you're only sure of 1 year, but at least if you were in a document someplace and you had some idea there would be a point at which it would be reviewed once that decision was made, you could continue your work.

Is there any research at the Bronx being done on how to construct a veterans' hospital? That was just a joke. [Laughter.]

Dr. Waxman, do you have anything to add to that?

Dr. WAXMAN. I agree that the system really at this point needs only fine tuning. I think most investigators view central office as being extremely supportive and doing a very good job with the resources at hand. I am not sure there are enough resources and what that translates into on issues of staffing and the stability of programs.

The kind of program that we all put together is a very fragile thing. You get the work going and one tries very hard to recruit the very best people one can. That is a very fragile balance.

Dr. Davis just mentioned DRG's, and I was surprised to see they were reverberating from your end of the country to mine. As a case in point, my program is in some ways boot-legged off of clinical activities. My salary is paid by clinical activities. Should the DRG situation threaten our funding level for clinical activities—and we're all very concerned that it might—we don't know if we'll have time to do research 1 year or 2 years from now. So that, plus the stability issue, what does one do with an extremely productive young scientist, who says, "I know we have gotten our grant every time we go through for renewal, but boy, I now would like something where I have a reasonable chance" because only 20 percent of them get funded. These are issues which we do worry about, and I think they are important issues.

Mr. EDGAR. Dr. Bernstein?

Dr. BERNSTEIN. I'm afraid I'm in the same boat as everybody else. I just lost a half-a-position, someone from my laboratory. It is going to cut our research back as well. I am a Ph.D., so I'm a little different than these gentlemen. I sit at the neck of an hourglass, with the bureacracy above me and young men and women who are mar-

ried, who have children, and just like you people must suffer every two years, they don't know where their children are going to go to school; they don't know if they're going to have their salaries. It is no way to run an operation. We must have stability. Anything that you can do to help that would aid us all.

Mr. EDGAR. Thank you. I appreciate all of your inputs.

I just have one final question. I do want to acknowledge David Waxman, who went over and helped me vote, who has been sitting in a back very patiently, waving his arms and saying it's time to end this hearing and stop asking questions, Mr. Chairman. But let me just ask one final question that I have to ask.

How do you cut waste, fraud, and abuse out of research projects that are silly, or researchers that begin to explore something in a 3-year research program and discover in the first year that they're barking up the wrong tree; they're floundering, or they're lazy, or not doing a good job; how do you pull the strings on a project that is not working very well when, in fact, you may need that researcher as a physician in the hospital and you don't want to offend them so they leave that setting?

Dr. BOREN. As you are indicating, this is a local problem. It comes back to the local R&D committee, the chief of staff and the clinical services of that hospital, that know the value and the function of the given person in question. They know the value of their researcher because each year we have a project data sheet that people have to send in, their annual progress report, plus it is pretty well known by the costaff members at any hospital as to who is being productive and who is being silly or being wasteful and not productive.

So it comes back to the wisdom of the local hospital R&D committee and the chief of staff to make arrangements in instances of potential abuse.

Mr. EDGAR. Dr. Boren, I'm not sure that is happening. I think that in some instances there may be some professionals who are doing some research that have some seniority and have some status and, you know, it is real hard to tell that person that maybe his research is not as productive as it needs to be.

I find, just in conversation with a few people in a couple of areas, that I really question whether or not it should be continued. I am not smart enough to know whether it should be, and I am sure there might be some additional need to review it from time to time.

I guess my hope is that we make the best use of the research dollars possible. We recognize their value, their magnetism for bringing scientists in and looking at some of these problems. I would hope that you might use this committee to give us your ideas and thoughts from time to time on specialized projects.

I mentioned to some of you that I am particularly interested in research of the brain, only because that's a fascination for me at this point. I think we have learned a lot about the brain in the last 5 years and we will learn a lot more in the next 5. I am looking both inside and outside the VA to understand how the brain operates, how it functions, what kind of contributions we can make to Alzheimer's disease, schizophrenia, what kind of contribution we can make to a broader realm of understanding how the brain func-

tions and operates. So any information you have on those issues would be very helpful.

Also, I chair the Congressional Clearinghouse on the Future, and as I indicated, Congressman Buddy MacKay is going to chair a task force on looking at ways to not only coordinate research activities in government, but getting the 185 committees and subcommittees of Congress to know what the right questions to ask are, because we don't have a battery of scientists and physicians who happen to be our staff people. We have lawyers and other professionals to help us with the language of law but not necessarily the content of research efforts. There is some interest in trying to balance out what looks, in just raw numbers, as though we're going to spend most of our research dollars on defense and not a lot of our research dollars on other areas of civilian and domestic research. For some of us who question some of the defense expenditures, who are nervous about that, even though there are some basic research spin-offs to the civilian side, we hope that there are some real commitments to research.

We appreciate the fact that the VA is committed to research, given its problems, and through our next two hearings we will explore this issue in even more depth and we hope to come to some understanding and perhaps even some new directions in our research themes.

Thank you all for your testimony. I appreciate it.

This hearing stands adjourned.

[Whereupon, at 12:25 p.m., the subcommittee was adjourned.]

APPENDIX

PARALYZED VETERANS OF AMERICA

CHARTERED BY THE CONGRESS OF THE UNITED STATES

STATEMENT OF

R. JACK POWELL, EXECUTIVE DIRECTOR

BEFORE

THE SUBCOMMITTEE ON HOSPITALS AND HEALTH CARE

OF

THE HOUSE COMMITTEE ON VETERANS' AFFAIRS

CONCERNING

VA MEDICAL RESEARCH PROGRAMS

ON NEUROLOGICAL DISORDERS

APRIL 26, 1984

Mr. Chairman and Members of the Subcommittee, Paralyzed Veterans of America appreciates this opportunity to express our views regarding the Veterans Administration's research programs on neurological disorders.

Neurological research is of critical importance to PVA's members, all of whom have experienced spinal cord injury or dysfunction. It is this research that holds for all SCI persons the greatest promise for improved physical well-being and, ultimately, an end to paralysis. The research efforts of the Veterans Administration, other federal agencies, and the private sector (including PVA's own research activities), all have made significant advances in neurological research during recent years.

It is because of the great importance that neurological research holds for our members and thousands of other disabled citizens, and the promise of such research, that we are especially grateful for this hearing today. It is hoped that the efforts of the VA and other research entities will receive greater public and government attention through such hearings. It is further hoped that increased resources and emphasis will be directed toward this vital and necessary field of research, which includes spinal cord regeneration.

One of the mandates of PVA's congressional charter is to promote research. Therefore, we are very proud of our organization's contributions to the growing field of spinal cord research that currently is expanding in this country, and we take our responsibilities in this area very seriously.

PVA's Spinal Cord Research Foundation was created in 1976, and at that time was called the PVA Technology and Research Foundation. In the past nine years, our Foundation has awarded more than $2.5 million to spinal cord research, including regeneration research.

I have brought with me today several brochures that explain PVA's involvement in spinal cord research, as well as copies of the December 1983, issue of the Paraplegia News, which summarizes some of the research efforts currently being sponsored by PVA. I urge you to read them and to contact PVA's Research Department if you have any questions.

In the field of spinal cord regeneration research, PVA would like to commend the VA for its efforts in this important area. Since 1980, the VA has

operated an Office of Regeneration Research at the VAMC in Portland, Oregon. This office serves as the VA's central coordinating point for regeneration research information. Through the efforts of Dr. Frederick Seil, Director of the Office of Regeneration Research, and the VA Central Office, regeneration research continues to be a "high priority" research area within the VA.

There are two major accomplishments of the VA's Regeneration Research program to which I would like to draw particular attention. First, that office has initiated a series of symposia which gathers together experts in fields related to regeneration, both within and outside the VA. These symposia have provided neuro-scientists with the opportunity to discuss face-to-face the work that they are doing, and to compare their findings. In doing so, they challenge one another's research techniques, and, most importantly, explore new ideas for future research. That is how progress occurs in a complex field such as this, and the VA has begun to take a leadership role in providing this type of exchange opportunity.

A second great accomplishment of the VA's Office of Regeneration Research has been the development of a quarterly publication, The Regeneration Research Newsletter. To our knowledge, it is the only regular newsletter on the topic of regeneration research, and thus fills a major void in the area of information dissemination. We would encourage the VA to continue publication of this newsletter and to expand it so that it becomes a primary resource for people involved in regeneration research.

From our contact with researchers in spinal cord research, it is clear that some of the most highly recognized leaders in this area are associated with

VA facilities. Dr. Stephen Waxman, for example, who is testifying here today, is a nationally-recognized figure in his field, and he also serves as a member of PVA's Scientific Advisory Board.

The disappointing fact remains, though, that so many other investigators in central nervous system regeneration are not affiliated with the VA. From our conversations with researchers, it appears that one of the major disincentives to working in the VA is the low level of research support available. In order to build a good laboratory within the VA, it is often necessary to utilize clinical funding as a supplement.

VA clinical personnel are well aware of the direct benefit research has for their patients. In the past they therefore have been quite willing to provide support for research from their clinical budgets. However, as demands on clinical services have increased, that sharing of resources has become less prevalent. This in effect represents a cutback in research funding.

The relationship between good patient care and good research has been stated many times, but it bears repeating. The way to attract qualified, inquisitive physicians and other staff to a VA hospital is to provide them with research opportunities. In turn, their research efforts can benefit both VA and non-VA patients in improved diagnostic and treatment techniques.

The field of regeneration research is one of the most compelling areas for the VA to be involved in, since the treatment of spinal cord injury was pioneered by VA physicians in the post World War II era. It would be most

fitting for the VA to lead the effort to cure this presently incurable condition. We urge Congress to provide the VA with the financial resources necessary to make spinal cord injury a condition of the past.

Mr. Chairman, the importance of the VA's efforts in neurological research, and particularly spinal cord regeneration research, cannot be overemphasized. We applaud the VA's continuing concern and commitment in this area and we hope that such efforts will grow and prosper to the benefit of the nation's veterans and all disabled individuals.

Mr. Chairman, this concludes my testimony and I will try to answer any questions that I can.

STATEMENT OF

JOHN A. GRONVALL, M.D.

DEPUTY CHIEF MEDICAL DIRECTOR

DEPARTMENT OF MEDICINE AND SURGERY

VETERANS ADMINISTRATION.

BEFORE THE

SUBCOMMITTEE ON HOSPITALS AND HEALTH CARE

COMMITTEE ON VETERANS' AFFAIRS

HOUSE OF REPRESENTATIVES

APRIL 26,1984

MR. CHAIRMAN AND MEMBERS OF THE COMMITTEE,
FIRST OF ALL, I WOULD LIKE TO THANK YOU AND THE OTHER MEMBERS OF THE SUBCOMMITTEE ON HOSPITALS AND HEALTH CARE FOR GIVING US THE OPPORTUNITY TO REPORT ON THE ACTIVITIES OF THE VETERANS ADMINISTRATION'S MEDICAL AND PROSTHETIC RESEARCH PROGRAM.

THE TOPICS TO BE DISCUSSED DURING THESE THREE HEARINGS -- NEUROLOGIC DISORDERS, PROSTHETICS, AND AGING -- HAVE PRIORITY STATUS IN THE VA RESEARCH PROGRAM, NOT ONLY BECAUSE THEY ARE OF PARTICULAR CONCERN TO THE VETERAN POPULATION WE ARE COMMITTED TO SERVE, BUT ALSO BECAUSE THEY REPRESENT SOME OF THE MOST DIFFICULT RESEARCH CHALLENGES FACING MEDICAL SCIENCE TODAY.

TODAY'S SESSION IS DEVOTED TO NEUROLOGIC DISORDERS -- ALZHEIMER'S DISEASE, SCHIZOPHRENIA, AND SPINAL CORD INJURY -- AND YOU WILL BE HEARING FROM FOUR VA INVESTIGATORS WHO ARE AT THE LEADING EDGE OF THE EFFORT TO SOLVE THE INCREDIBLY COMPLEX PROBLEMS THAT THESE DISORDERS REPRESENT.

FACING -- AND OVERCOMING -- DIFFICULT CHALLENGES IS NOT NEW TO VA INVESTIGATORS. WE HAVE A PROUD TRADITION OF ACCOMPLISHMENTS THAT HAVE BEEN OF BENEFIT NOT ONLY TO VETERAN HEALTH CARE BUT TO THE U.S. HEALTH CARE SYSTEM AS A WHOLE.

FORTUITOUSLY, THE TIMING OF THESE HEARINGS COINCIDES WITH THE RELEASE OF A NEW PUBLICATION THAT CHRONICLES SOME OF THOSE CONTRIBUTIONS.

"MEDICAL ADVANCES: THE VA'S CONTRIBUTION TO U.S. HEALTH CARE" IS NOT DESIGNED TO TOOT OUR OWN HORN OR EVEN TO JUSTIFY OUR EXISTENCE. INDEED, THE IMPETUS FOR ITS PUBLICATION CAME FROM OUTSIDE THE VA: FROM REPRESENTATIVES OF VETERAN SERVICE ORGANIZATIONS WHO FELT THAT AN IMPORTANT PART OF THE VA STORY WAS NOT BEING TOLD.

WITHIN THESE PAGES YOU WILL FIND ACCOUNTS OF PAST ACCOMPLISHMENTS AND CURRENT EFFORTS TO PUSH BACK THE

FRONTIERS OF MEDICAL KNOWLEDGE. SUCH CONTRIBUTIONS INCLUDE:

o DEVELOPMENT OF THE DRUG TREATMENT THAT HELPED WIPE OUT TUBERCULOSIS AS A MAJOR PUBLIC HEALTH MENACE;

o DEVELOPMENT OF DRUG TREATMENTS THAT MADE IT POSSIBLE FOR THOUSANDS OF PATIENTS WITH MENTAL ILLNESS TO FUNCTION IN SOCIETY;

o MAJOR CONTRIBUTIONS TO SOLVING THE TECHNICAL AND MEDICAL PROBLEMS OF ORGAN TRANSPLANTS;

o DEVELOPMENT OF THE THEORETICAL CONCEPT THAT LED TO COMPUTERIZED TOMOGRAPHY -- THE CAT SCAN; AND,

o DEVELOPMENT OF THERAPEUTIC TECHNIQUES FOR THE CONTROL OF HYPERTENSION.

AND SINCE THERE ARE FEW HEALTH PROBLEMS THAT DO NOT TOUCH THE LIVES OF THE MEN AND WOMEN WHO HAVE SERVED IN OUR NATION'S ARMED FORCES, THERE ARE FEW RESEARCH AREAS THAT ARE UNTOUCHED BY VA INVESTIGATORS.

HOWEVER, THE BOOK IS MORE THAN A CATALOGUE OF RESEARCH SUCCESSES. IT TRACES THE DEVELOPMENT OF THE NATION'S LARGEST HOSPITAL SYSTEM AND THE CREATION OF A CLIMATE IN WHICH SUCH SUCCESSES ARE POSSIBLE: A CLIMATE IN WHICH A CLINICIAN CAN CONDUCT RESEARCH THAT IS DIRECTLY RELATED TO THE PROBLEMS OF HIS PATIENTS.

THIS, IN TURN, IS RELATED TO THE EARLY CONGRESSIONAL RESPONSE TO THE NEEDS OF RETURNING WORLD WAR II VETERANS, THE LEADERSHIP OF SUCH MEN AS GENERALS OMAR N. BRADLEY AND PAUL R. HAWLEY. IT IS LINKED ALSO, TO THE FORESIGHT OF SUCH PHYSICIANS AS PAUL B. MAGNUSON AND WILLIAM S. MIDDLETON, WHO RECOGNIZED THAT A VIABLE, QUALITY CARE SYSTEM CANNOT EXIST UNLESS RESEARCH AND EDUCATION SERVE ALONGSIDE THE PROVISION OF CARE ITSELF.

THE BOOK MAY BE FINISHED, BUT THE STORY IS NOT. IT CONTINUES IN THE TESTIMONY YOU WILL HEAR TODAY AND IN THE WEEKS TO COME.

THAT CONCLUDES MY STATEMENT, MR. CHAIRMAN. I WILL BE PLEASED TO ANSWER ANY QUESTIONS YOU OR MEMBERS OF THE COMMITTEE MAY HAVE.

STATEMENT OF

HOLLIS G. BOREN, M.D.

ASSISTANT CHIEF MEDICAL DIRECTOR

RESEARCH AND DEVELOPMENT

DEPARTMENT OF MEDICINE AND SURGERY

VETERANS ADMINISTRATION.

BEFORE THE

SUBCOMITTEE ON HOSPITALS AND HEALTH CARE

COMMITTEE ON VETERANS' AFFAIRS

HOUSE OF REPRESENTATIVES

APRIL 26, 1984

MR. CHAIRMAN AND MEMBERS OF THE COMMITTEE
I AM VERY PLEASED TO HAVE THE OPPORTUNITY TO APPEAR
BEFORE YOU TODAY. MY TASK IS TO PROVIDE SOME BACKGROUND
AND TO INTRODUCE THE VA INVESTIGATORS WHO WILL BE TESTIFYING.

DR. GRONVALL TOLD YOU THAT THE TOPICS TO BE DISCUSSED AT THESE
HEARINGS REPRESENT SOME OF THE MOST DIFFICULT CHALLENGES
FACING MEDICAL SCIENCE TODAY. THEY CERTAINLY ARE.

IN TODAY'S HEARING, FOR EXAMPLE, WE WILL CONCENTRATE ON VA
RESEARCH EFFORTS RELATED TO ALZHEIMER'S DISEASE,

SCHIZOPHRENIA, AND SPINAL CORD INJURY --THREE OF THE MOST DEVASTATING OF HUMAN DISORDERS.

THE TRAGEDY OF THESE CONDITIONS IS THAT WHILE THEY DO NOT KILL, THEY ARE TRULY LIFE-SHATTERING -- BOTH FOR THE VICTIMS AND FOR THEIR FAMILIES, ALL OF WHOM MUST LEARN TO COPE WITH THE EFFECTS OF DRASTIC PHYSICAL OR MENTAL CHANGES.

FOR THE PHYSICIAN, THESE CONDITIONS ARE FRUSTRATING BECAUSE THE ANSWERS ARE LOCKED INSIDE AREAS ABOUT WHICH WE STILL HAVE MUCH TO LEARN; THE MIND AND THE CENTRAL NERVOUS SYSTEM. AS A RESULT, CURRENTLY AVAILABLE TREATMENT FOR ALL THESE DISORDERS IS AT BEST, PALLIATIVE.

THE VA'S INTEREST IN THESE AREAS STEMS FROM THE LARGE NUMBERS OF PATIENTS ADMITTED TO OUR HOSPITALS FOR TREATMENT. THE RESEARCH EFFORT IS A NATURAL OUTCOME OF THE CLOSE CONNECTION BETWEEN CLINICAL PROBLEMS AND RESEARCH ENDEAVORS THAT IS ONE OF THE HALLMARKS OF THE VA RESEARCH PROGRAM.

ALZHEIMER'S DISEASE IS A DEGENERATIVE, PROGRESSIVE DISORDER IN WHICH THE DESTRUCTION OF BRAIN CELLS ROBS THE PATIENT FIRST OF MEMORY, THEN OF REASON. THE INCREASING FREQUENCY WITH WHICH THIS CONDITION IS BEING SEEN HAS MADE ALZHEIMER'S A HOUSEHOLD WORD.

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IN 1982, ALZHEIMER'S DISEASE WAS RESPONSIBLE FOR MORE THAN 22,000 DISCHARGES FROM VA HOSPITALS AND MORE THAN 5000 DISCHARGES FROM EXTENDED CARE FACILITIES. OF EVEN GREATER CONCERN, HOWEVER, IS THE PROJECTION THAT BETWEEN 1980 AND THE END OF THE CENTURY, THE INCIDENCE OF ALZHEIMER'S DISEASE WILL TRIPLE.

TODAY, DR. KENNETH L. DAVIS, CHIEF OF PSYCHIATRY AT THE BRONX VA MEDICAL CENTER, WILL PRESENT SOME OF THE PROMISING EARLY FINDINGS OF HIS RESEARCH INTO ALZHEIMER'S DISEASE.

HE WILL ALSO REPORT ON HIS WORK ON SCHIZOPHRENIA -- A DISABLING CONDITION THAT AFFECTS ONE OUT OF EVERY SIX PATIENTS IN VA HOSPITALS. ON OUR PSYCHIATRIC WARDS, 84 PER CENT OF THE PATIENTS HAVE BEEN DIAGNOSED AS SCHIZOPHRENIC. BECAUSE OF THE MAGNITUDE OF THE PROBLEM, THE VA ESTABLISHED, IN 1981, TWO SCHIZOPHRENIA BIOLOGICAL RESEARCH CENTERS (SBRC), ONE IN THE PALO ALTO VA MEDICAL CENTER AND THE OTHER IN THE BRONX VA MEDICAL CENTER.

AS DIRECTOR OF THE BRONX SBRC, DR. DAVIS WILL REPORT ON SOME OF THE SIGNIFICANT RESEARCH EFFORTS BEING CONDUCTED IN THE AREA OF SCHIZOPHRENIA.

THE FINAL TOPIC YOU WILL HEAR ABOUT TODAY IS SPINAL CORD REGENERATION -- PERHAPS THE MOST DIFFICULT OF ALL THE

RESEARCH CHALLENGES CURRENTLY BEING ADDRESSED.

SPINAL CORD INJURY IS USUALLY ACCIDENT-RELATED AND THE VICTIMS TEND TO BE YOUNG ADULTS. IT IS RARELY FATAL, AND MEDICAL TREATMENT HAS EXTENDED THE LIFE EXPECTANCY OF SCI PATIENTS CONSIDERABLY. NEVERTHELESS, THE TRAGEDY AND THE ECONOMIC IMPACT ON THE VICTIM, THE FAMILY, AND SOCIETY IS PROFOUND.

THE VA HAS 19 SPINAL CORD INJURY CENTERS WITH A TOTAL BED CAPACITY OF 1353. DURING THE PERIOD FROM FY1976 THROUGH FY1982, A TOTAL OF 18,218 INDIVIDUAL PATIENTS WERE TREATED.

TODAY, DR. STEPHEN G. WAXMAN, CHIEF OF THE NEUROLOGY SERVICE AT THE PALO ALTO VA MEDICAL CENTER WILL GIVE AN OVERVIEW OF SPINAL CORD INJURY RESEARCH AND ITS PROGRESS TO DATE.

DR. JERALD J. BERNSTEIN, CHIEF OF THE LABORATORY OF CENTRAL NERVOUS SYSTEM INJURY AND REGENERATION AT THE WASHINGTON D.C. VA MEDICAL CENTER, WILL DESCRIBE HIS WORK WITH SPINAL CORD TRANSPLANTS.

FINALLY, DR. FREDERICK SEIL WILL DESRIBE THE WORK OF HIS OFFICE OF REGENERATION RESEARCH AT THE PORTLAND VA MEDICAL CENTER, AND GIVE HIS PERSPECTIVE ON THE FUTURE OF RESEARCH

IN SPINAL CORD REGENERATION.

THAT CONCLUDES MY STATEMENT, MR. CHAIRMAN. IF YOU OR ANY OTHER MEMBERS OF THE COMMITTEE HAVE ANY QUESTIONS, I WILL BE PLEASED TO ANSWER THEM.

Statement of

KENNETH L. DAVIS, M. D.

Chief, Psychiatry Service

Veterans Administration Medical Center, Bronx
and
Professor of Psychiatry and Pharmacology
Mt. Sinai School of Medicine

before the

Subcommittee on Hospitals and Health Care
Committee on Veterans Affairs
House of Representatives

April 26, 1984

Mr. Chairman and Members of the Committee: Thank you for the opportunity to speak before you here today. I would like to talk to you about the research that we have been conducting in Alzheimer's disease and schizophrenia, two health problems affecting millions of Americans well known to this committee, as well as the implications of this work for the care of our veterans.

A series of studies conducted in the United Kingdom in 1976 and 1977 reached an extraordinary conclusion about Alzheimer's disease. Three laboratories working independently reported that in Alzheimer's disease, there was a loss of brain cells that made the neurotransmitter acetylcholine. This conclusion was based upon the discovery that the enzyme which synthesizes acetylcholine, and is only found in brain cells that make acetylcholine, (i.e. cholinergic neurons) was very much reduced in the brains of patients with Alzheimer's disease.

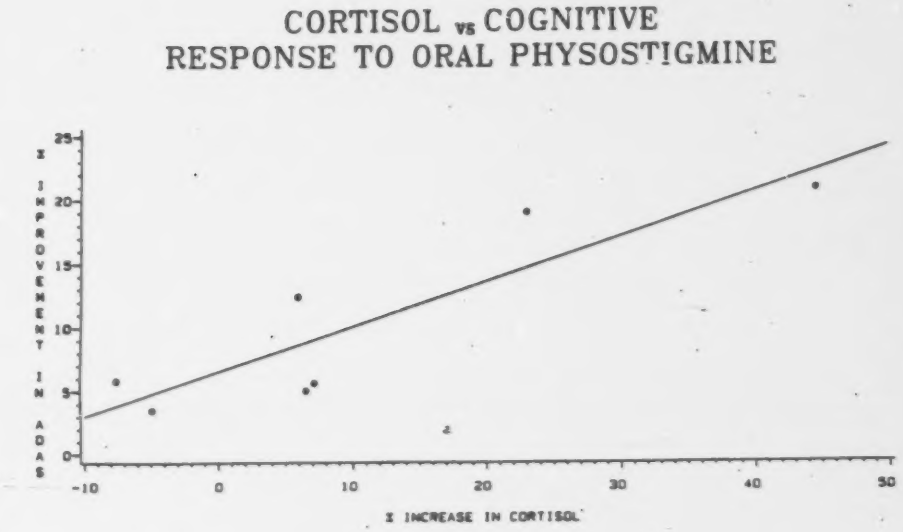
This finding led a number of research groups including, our own at the Bronx VA, to suggest that a possible treatment for Alzheimer's disease would be a drug that could increase brain cholinergic activity. Such an attempt was particularly appropriate to our research ward, because we had been investigating a drug that increases brain acetylcholine, physostigmine. Physostigmine inhibits the breakdown of acetylcholine. In fact, while neurochemists in the United Kingdom were finding that the brains of patients with Alzheimer's disease had a cholinergic deficit, our laboratory was conducting a study of the effects of physostigmine on memory in young normal people. We found that the administration of this drug to young normal people could improve their ability to remember new information. The simultaneous discovery of the acetylcholine deficiency in patients with Alzheimer's disease, and the ability of drugs that increased brain acetylcholine to enhance memory, led to the idea that the memory disorder in Alzheimer's disease

might be improved with drugs like physostigmine.

With the help of a program project grant from the National Institute of Aging, as well as support from the Veterans Administration, my colleague Richard Mohs and I began a study of physostigmine in Alzheimer's disease. We first administered an intravenous form of the drug and then an oral preparation. The initial studies with intravenous physostigmine were encouraging, although the ability of physostigmine to improve memory was hardly as robust as one might have hoped. Still additional studies were necessary, because intravenous physostigmine is so short acting that it was impossible to adequatley assess whether the drug would help patients in daily life.

Studies with oral physostigmine have begun. However, there is very good reason to believe that not all patients with Alzheimer's disease will respond to this drug, nor will all patients who respond to physostigmine respond in the same way. This problem arises from the fact that for physostigmine, which prevents the breakdown of existing acetylcholine, to work, the brain must be able to synthesize some acetylcholine. Unfortunately, as the disease progresses cells which synthesize acetylcholine are dying. Because of this problem we needed some way, besides memory testing, to be sure the physostigmine was getting into the patients brains, and that those brains could still make some acetylcholine for the physostigmine to preserve. In collaboration with an endocrinologist in our laboratory, Dr. Bonnie Davis, we have found that when physostigmine enters the brain, and acetylcholine containing cells are available to synthesize adequate quantities of acetylcholine, then physostigmine increases the amount of cortisol the patient's body secretes at night. The effect of physostigmine to increase nocturnal cortisol concentrations correlates with the drug's ability to improve the symptoms of AD, as the figure below indicates. These results support the notion that physostigmine only improves the cognitive functioning in those patients whose

acetylcholine containing neurons have not yet been devastated by the disease.



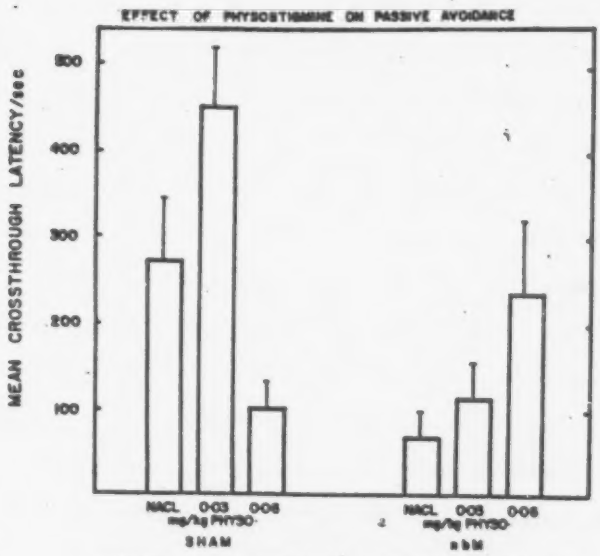
$r=.88 \quad p < .01$

Although these results are encouraging to the scientist, for the patient with Alzheimer's disease the effects are not as impressive or uniform as one would desire. Instead they only point to other directions that must be pursued and better drugs that must be developed. Nonetheless, these results, which have been replicated in other laboratories, indicate that current approaches are rational.

Given these effects of physostigmine, as well as results from other researchers, there now is a need to identify those Alzheimer's patients who may be made modestly less demented by therapies that increase brain acetylcholine. A cooperative study has been proposed by Richard Mohs and myself, as well as medical scientists from a number of other VAs, to determine the ultimate clinical utility of physostigmine. We are hopeful that it will be funded, and over the next five years may be able to ascertain just what segment of the Alzheimer's population may be benefited by physostigmine. Such a study can only be done through the cooperative studies program at the Veterans Administration. It will require extensive coordination of the large study population that is made available by the health care delivery system in the Veterans Administration. The cooperative studies program has produced invaluable studies of the effects of treatment of high blood pressure, and prostate cancer, yielding information which has saved lives, prevented disability, and saved health care dollars.

Whatever the results of the VA cooperative study, it is clear that not all patients are going to be helped by physostigmine treatment, and that those patients who are helped will not be returned to a normal life. For that reason additional work is necessary. To that end our program has been engaged in developing an "animal model" of Alzheimer's disease that may expedite development of other drugs. These studies are made possible by a merit review grant from the VA to me and my colleague, Dr. V. Haroutunian as well as collaboration with the Hoechst Roussel Pharmaceutical Corporation. Together we have found that destruction of a tiny part of the rat's brain can produce a deficit in acetylcholine that in many ways resembles the deficit that exists in AD. This rat model makes possible the screening of drugs for their ability to improve the memory of "demented" animals.

The figure below illustrates how physostigmine, the drug we are administering to



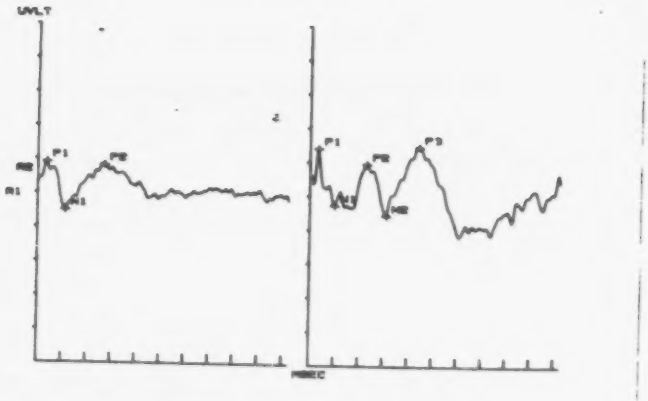
Effects of post-acquisition physostigmine administration on the 72 hour retention of passive avoidance in abM lesioned and sham operated rats.

humans, can reverse the abnormal behavior that animals with a cholinergic deficit exhibit. In the future new drugs that might be more efficacious will be tested, and more importantly, the model will be extended so that it even more closely resembles the human condition. In addition, with the help of funding from the VA we are now transplanting brain tissue to these lesioned animals in the hope of normalizing their behavior. This will be a difficult process but one with obvious implications for developing a treatment for Alzheimer's disease.

A real problem in Alzheimer's disease research is the difficulty in making this diagnosis with absolute certainty. At present a definitive diagnosis of Alzheimer's

disease is only made at autopsy by examining the brain under the microscope, or with the help of a biopsy. Rarely are biopsies performed, thus some uncertainty inevitably exists when a clinical diagnosis is made. For that reason our program, with the help of funding from the NIA and the VA has been searching for a clinical test for Alzheimer's disease that would facilitate a diagnosis prior to autopsy.

The figure below is a representation of electrical activity recorded from the



scalp when normal people hear a series of similar tones (left panel). These wave forms can be generated and recorded with uncanny reliability. However, as the panel on the right indicates when similar tones are interrupted by a different tone, additional waves appear. The table below illustrates that patients with Alzheimer's disease show a very different electrical response to those tones than normal elderly.

Discriminant Function Coefficient	
P2 Latency to "Frequents"	-0.41
N2 Latency to "Rares"	0.62
P3 Latency to "Rares"	0.49
P3 Amplitude to "Rares"	-0.43

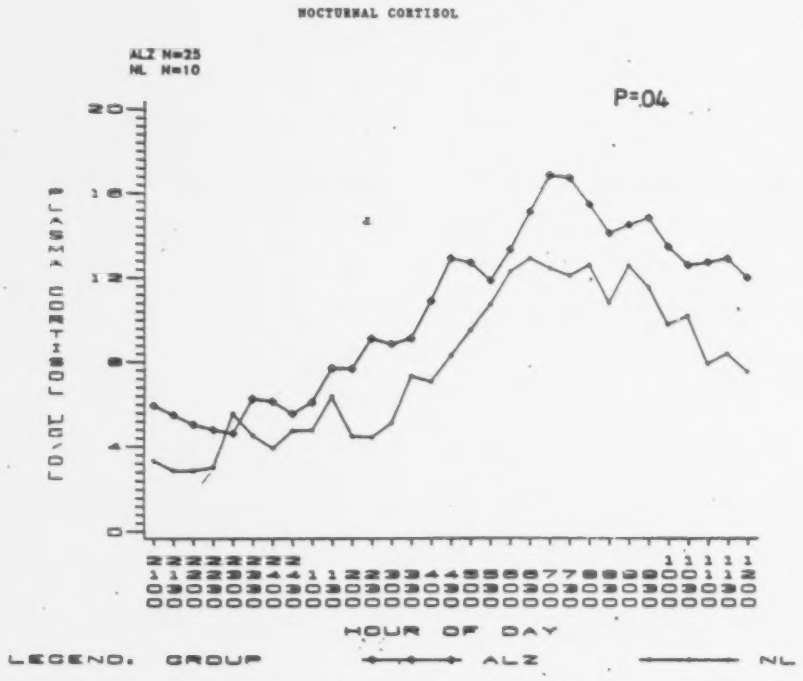
Actual Group	N	Predicted Membership	
		Correct:	Incorrect:
Alzheimer's	12	12	0
Controls	16	15	1

Percent of "grouped" cases correctly identified: 96.4%

We have so far been very accurate in using these measurements of electrical activity to classify patients as having Alzheimer's disease or being without dementia. This is not the same as saying that this technique can differentiate Alzheimer's patients from patients with other forms of dementia, but it is at least an encouraging first step. The principal investigator in these studies is Dr. Thomas

Horvath and his ability to carry them out is the result of the "innovative aging initiative" the VA sponsored last year. The data that he has so far generated encourages us to look at scalp electrical activity in far more depth to determine if it might be a diagnostic marker of Alzheimer's disease.

Another possible marker are concentrations of plasma cortisol in blood. The pattern of nocturnal cortisol secretion, as shown in the figure below, is higher in



patients with Alzheimer's disease than normal elderly people of roughly the same age. Other aspects of cortisol secretion seem equally unusual. For example, cortisol in a single sample of blood taken at 9:00 a.m. was in fifteen or sixteen instances higher in Alzheimer's patients than in age and sex matched normal persons. These abnormalities also suggest that measurements of cortisol may help differentiate Alzheimer's, from normal people, and perhaps other forms of dementia. However, it is important to emphasize that these are initial studies and require much more work before we can take them as definitive.

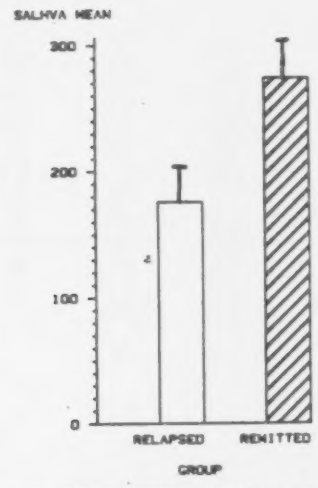
Schizophrenia remains one of the most complex problems that clinical neuroscientists confront. It is a disabling condition with an onset in early adulthood that persists throughout life. The cost to the patient, famiy and society is enormous. To the VA this problem is particularly acute as so many of the VA beds are devoted to the treatment of people who are affected by this disease. Thus, a major effort is needed to understand and treat this disorder.

In 1981, the VA launched a new program in schizophrenia research. Following a national competition, a Schizophrenia Biological Research Center (SBRC) was established at the Bronx VA, to investigate the biological basis of schizophrenia. The first grant to the Center began in January 1981 and will end in 1986, unless otherwise renewed. I am the director of the SBRC of the Bronx VA. In 1982, a parallel center was inaugurated at the Palo Alto VA Hospital under the direction of Drs. Phillip Berger and Tom Roth.

The chemical in the brain most commonly thought to cause or worsen schizophrenia is dopamine. Although some aspects of schizophrenia can not be explained by this neurotransmitter, many other aspects of the syndrome implicate this compound. The major breakdown product of dopamine in the brain is a compound called homovanillic acid, (HVA) which can be measured in spinal fluid. We measured HVA in a group of schizophrenic patients whose illness was in

remission, and in another group of schizophrenic patients who were quite ill. The figure below demonstrates that HVA concentrations in the cerebrospinal fluid of ill schizophrenics was lower than in the group in remission. Although there were

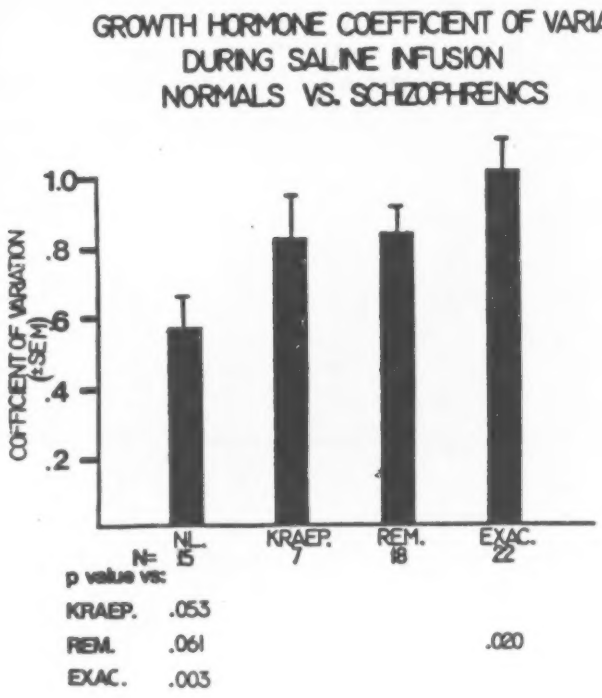
CSF HVA AFTER SALINE IN REMITTED AND RELAPSED SCHIZOPHRENICS (N=24)



P=.03 BY ANCOVA COVARYING FOR AGE AND WEIGHT

many possible interpretations of these results, they strongly suggest that changes in the functioning of dopamine containing neurons may be associated with the critical behavioral changes that occur when schizophrenics move from a state of remission to illness. Obviously, understanding the cause of fluctuations in the disease could shed light on the cause of the disease itself.

We have sought other chemical differences between schizophrenic patients who are ill and those in remission. As the figure below illustrates growth hormone



concentrations were associated with greater fluctuations and more abnormal bursts of activity when patients were ill than when patients were in remission. Furthermore, even schizophrenics in remission had more erratic and unexplainable growth hormonal activity than did the normal population. Thus, there seemed to be more disorganized growth hormone secretion in ill schizophrenics than in improved schizophrenics, an in well schizophrenics than in normal persons. More is known about the chemical control of hormones than of schizophrenic behavior, so it may be possible to identify the chemical abnormality in schizophrenia by studying

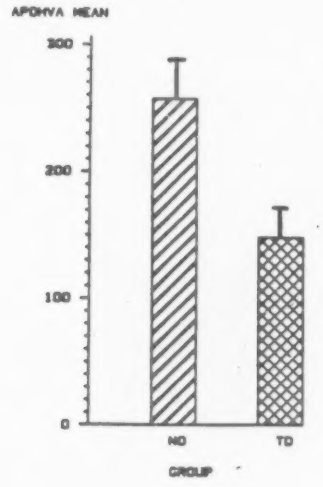
schizophrenic's hormonal abnormalities, and use that to better understand the behavior.

Short of the idealistic goal of identifying the chemical basis of schizophrenia, we are working on some more specific and more immediately clinically useful tests.

One unfortunate side effect of antischizophrenic drugs is tardive dyskinesia. This syndrome, consisting of uncontrollable, almost continuous tics and small movements of the mouth, hands and legs, makes life even more difficult for the schizophrenic. It is permanent in 10-20% of VA patients and has been the subject of national news programs.

Tardive dyskinesia is thought to be due to a form of drug-induced chemical changes to dopamine-containing areas, making them overly sensitive. The experiment shown below is an indirect way of demonstrating increased sensitivity

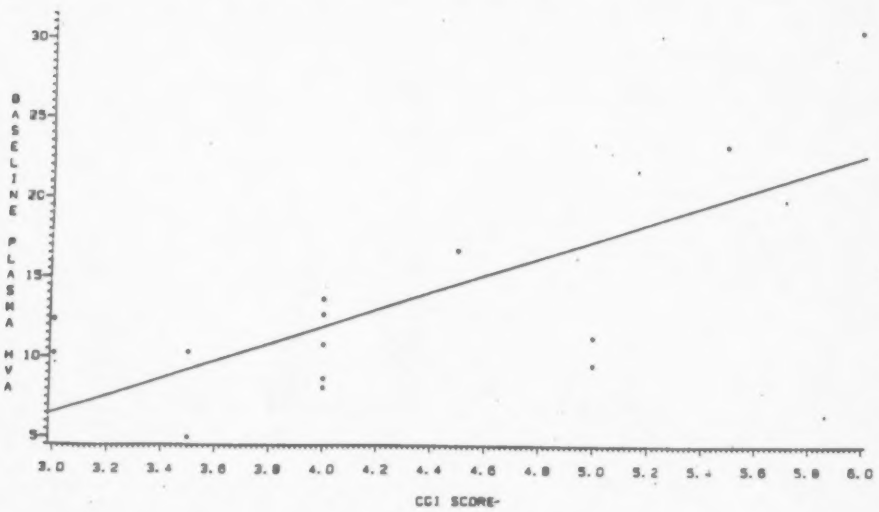
CSF HVA AFTER APOMORPHINE
IN TARDIVE DYSKINESIA (N=22)



to dopamine in actual patients with tardive dyskinesia. The body responds to high levels of dopamine by turning off dopamine production, resulting in lowered cerebrospinal fluid HVA. In patients with tardive dyskinesia, increased sensitivity to a dopamine-like drug that was given resulted in an accentuated fall in HVA in patients with tardive dyskinesia as compared to patients without tardive dyskinesia. While this information is not yet a solution, it is one of the building blocks on which an effective treatment or preventitive measure would be based.

A second problem of major clinical proportions is the large cadre of VA patients who are treatment-resistant. These patients are chronically-hospitalized at the expense of the system and are unable to lead productive lives. If such patients differed chemically from patients responsive to current drugs, then identification of the differences might lead to development of drugs that would be effective for them. We gave a test dose of an antipsychotic drug to a series of patients. These drugs block dopamine, so the body responds by increasing production of dopamine and subsequently HVA. The figure shows that patients with

CORRELATION OF BASELINE PLASMA HVA WITH DAY 29 POST-HALOPERIDOL CLINICAL GLOBAL IMPRESSION SCORE

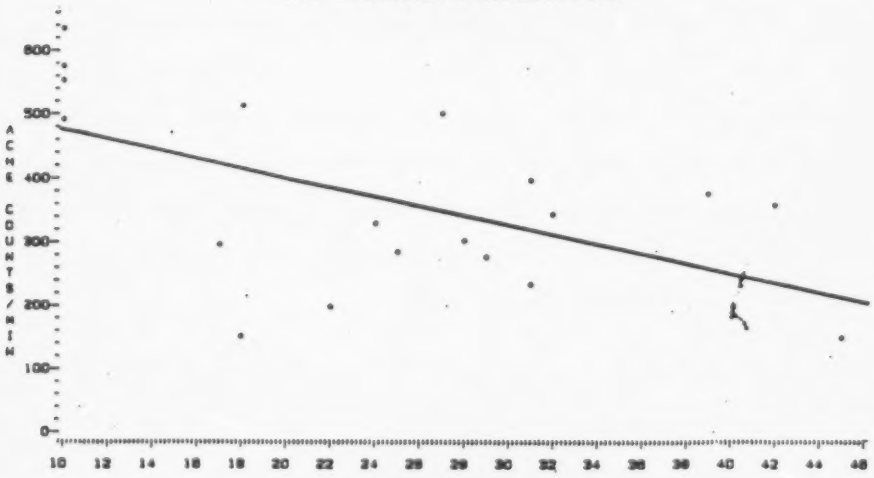


r=.73,p=.006 n=14

the largest HVA values, that is, the greatest chemical response, had the poorest response to treatment. These results rule out the most simpleminded explanation for drug failure, namely, that the drug has little biochemical effect. They lead us to consider other possibilities. For instance, the nonresponders could have no disease at all in the brain dopamine system. Subsequent studies will evaluate these possibilities and take us a little closer to helping these patients.

An extremely troubling aspect of the schizophrenic syndrome is the fact that after the more prominent symptoms, such as hallucinations, delusions and illogic are brought under control by drugs, patients are still often unable to reintegrate into the community. Asocial behavior, apparent lack of motivation, and an inability to experience pleasure, all contribute to the schizophrenic's problem. These difficulties can be so profound that it has been suggested for many years that schizophrenic patients have a subtle form of dementia that may progress as the disease goes on. With that possibility in mind, we have been particularly struck with the finding reflected in the figure below.

CORRELATION OF CSF ACHE AND NEGATIVE SYMPTOMS IN SCHIZOPHRENICS



AGE AND CSF PROTEIN CORRECTED r=-.56 p=.02 n=19

These data demonstrate that as patients have more of these symptoms of schizophrenia outlined above, which are referred to as negative symptoms, they seem to have a loss of activity of an enzyme called acetylcholinesterase in their cerebrospinal fluid. In patients with Alzheimer's disease, diminished acetylcholinesterase activity has been linked to dementia. It is possible that those schizophrenic patients with the most profound negative symptoms may also have the greatest loss of cholinergic activity. This idea is consistent with the notion that the schizophrenic syndrome may, in its late and more profound states, be a subtle form of dementia. Should this be the case, a number of treatment options previously not considered can be conceptualized, which could have the ability to improve the performance of schizophrenics in the community. However, until additional data is gathered these ideas remain speculations.

As to future research in schizophrenia, procedures are now available that could provide new insights into the disease. The use of imaging techniques such as nuclear magnetic resonance and positron emission tomograpy are just being applied to the study of schizophrenia. Similarly, the kinds of sophisticated analyses that have been carried out on autopsy material of patients with Alzheimer's disease can be conducted in patients with schizophrenia. Finally, it seems not impossible that the concepts being developed in molecular genetics may prove useful in unraveling this disorder. However, whether these, or other more traditional approaches ultimately help us to understand and treat schizophrenia, the vision reflected in the Veterans Administration's decision to establish schizophrenia biological research centers will surely contribute to the understanding of the biology of schizophrenia. These centers remain the only government funded programs outside the NIH solely dedicated to researching this disabling condition.

I would like to conclude by discussing the impact of medical research to the clinical care of veterans. As both a chief of psychiatry and the principal investigator of many of the projects discussed today, I believe I have a unique perspective on the impact of clinical investigation for the quality of care veterans receive.

The Psychiatry Service at our hospital now has the highest possible JCHA accreditation. The occupancy rate exceeds 90%. Patient satisfaction surveys show a high degree of satisfaction with the program. Both internal and external reviews have been lauditory. Our residency program has grown and is completely integrated with the medical school and there are no vacancies in the residency program. Every staff physician position is filled with high quality people including a number of individuals who have not just M.D.s but M.D. and Ph.D. degrees. Our staff comes from the NIH, Yale, Harvard and Stanford. Our patients receive the most modern tests and treatments. These improvements could not have occurred without making research part of clinical care. It was only though a high quality research program funded through the VA and NIH that we were able to recruit physicians to our service. A program in clinical investigation was the main impetus for the medical school to jointly recruit residents, and thereby improve the quality of the house staff in our program. The respect that our program has generated within the hospital is reflected in the attitude of almost all the health professionals and nurses who come in contact psychiatric patients.

If I can leave you with one impression today, it is that, the funds the VA appropriates to its research program produces benefits that are many times as great as the actual allocation. I could not retain my staff without the VA's research program. Rarely does a program spend less and obtain more than the VA's research program.

This concludes my statement. I would be pleased to answer any questions that you or members of the Committee may have.

STATEMENT OF

STEPHEN G. WAXMAN, M.D., Ph.D.

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Veterans Administration Medical Center, Palo Alto
and
Professor and Associate Chairman,
Department of Neurology;
Chairman, Neurosciences Program,
Stanford University School of Medicine

before the

Subcommittee on Hospitals and Health Care,
Committee on Veterans Affairs,
House of Representatives

April 26, 1984

Mr. Chairman and Members of the Committee: Thank you for the opportunity to speak before you here today. I would like to speak about research on neurological diseases within the Veterans Administration. This is a very exciting time for the neurosciences, but we face some major challenges. I would like to speak about the problem of recovery following injury to the nervous system, and to discuss some of the progress that has been made, the prospects for further advances, and the problems we face. In particular, I would like to briefly discuss the ways that the nervous system responds to injury, and some of the approaches that have been taken to the study of regeneration of nerve cells.

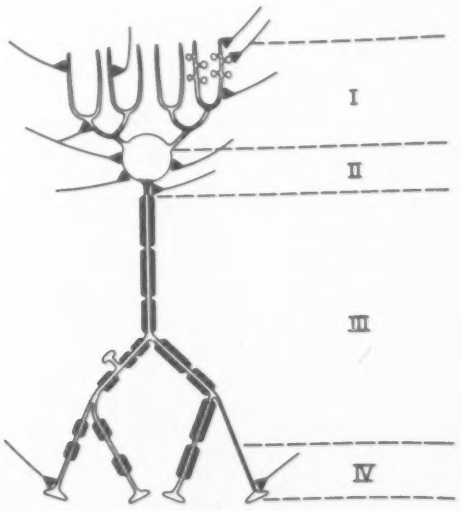
The Veterans Administration has a very deep and long-standing interest in injury to the brain and spinal cord. There are, for example, more than 100,000 individuals paralyzed from spinal cord injury, alive in the United States at this time. While longevity has improved substantially due to significant improvements in symptomatic care (e.g. in terms of treatment of decubiti, urinary tract infections, etc.), we still can only palliate or support these patients, and in fact, do not at present offer therapies which

might cure or effectively reverse paralysis from spinal cord injury. Similarly, we still do not have effective therapies which might reverse the neurological deficits in patients with cerebrovascular and similar disorders.

At the same time, it has become clear that the nervous system can respond adaptively to injury, and that we may be able to harness, in the clinical domain, some of the mechanisms of plasticity by which the nervous system reorganizes following various disease insults.

I will take the liberty of showing you some simple diagrams which outline the problem, and introduce some of the approaches which have been taken with respect to this area.

Figure 1.



The nervous system is comprised of nerve cells (neurons) and supporting (glial) cells. Figure 1 is a diagram of the nerve cell. The receptive pole, where it receives information from other nerve cells, is labelled as component "I". The cell body, which can be thought of as containing the genetic code and the metabolic machinery of the nerve cell, is component "II". This part

of the cell serves to integrate incoming neural signals. The nerve fiber or axon (component "III") serves as a transmission line for the electrical signals by which neurons communicate. Within the spinal cord, descending and ascending axons function as the conduits for communication between brain and lower motor-sensory centers for the limbs, bladder, etc. When the integrity of nerve fibers within the spinal cord is interrupted, the brain cannot communicate with lower areas. This results in paralysis, sensory loss, spasticity, loss of bowel and bladder control, etc.

There is now a large body of evidence which indicates that, following damage to an axon in peripheral nerve, the axon will often regenerate, so as to reach its proper target and establish new (and functional) connections. In contrast, following damage to an axon in the central nervous system (brain and spinal cord), regeneration does not normally occur to any great extent. Nevertheless, we are beginning to learn about recovery following injury to nerve cells in the central nervous system, and there is good reason to expect that a significant degree of functional recovery can be promoted in some patients following injury.

Figure 2.

One disease that serves as an important model in this respect is multiple sclerosis. This is a disorder in which central axons lose their myelin sheaths (which serve as insulation). Figure 2 shows a section from the brain of a patient with multiple sclerosis. The white areas represent demyelinated lesions in which the nervous system has sustained damage. Following this damage, there are often profound neurological deficits. Of considerable interest, however, is the fact that functional recovery occurs in some patients with multiple sclerosis, during clinical remission.

Notably, this recovery of function occurs in the face of fixed structural damage. The important point here is that nerve cells and their supporting cells exhibit plasticity, at both the cellular and subcellular levels. This plasticity permits the nervous system to reorganize following an episode of multiple sclerosis, in such a way as to permit recovery of function (the clinical remission). In the case of demyelinating diseases such as multiple sclerosis, we are on the verge of understanding the cellular basis for remission. In this respect, I have attached a recent article from the New England Journal of Medicine ("Current Concepts in Neurology: Membranes, Myelin, and the Pathophysiology of Multiple Sclerosis," Vol. 306, pages 1529-1533, June 24, 1982) which reviews recent progress in this important area. The occurrence of remissions in multiple sclerosis leads us to believe that it is not unreasonable to expect a degree of neural plasticity which permits some functional recovery following insults such as spinal cord injury.

It is known that, following injury to an axon within the spinal cord or brain of mammals, regeneration does not usually occur to any great extent. But in contrast to this, nerve fibers do regenerate quite briskly (and in many cases quite effectively) following injury to peripheral nerve. Considerable progress has been made in terms of understanding this process.

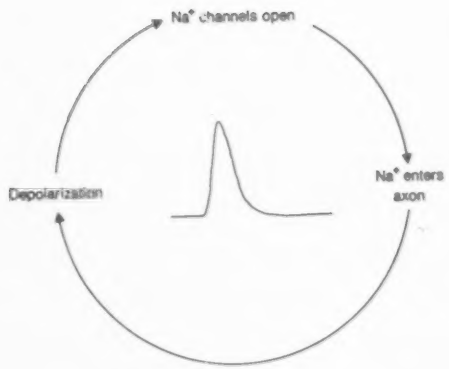
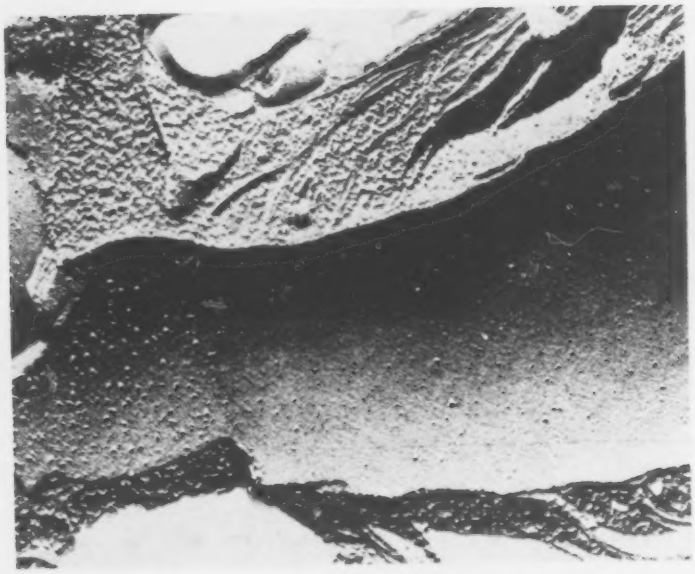


Figure 3.

We have begun, for example, to understand the basis for the transmission of information in the normal and pathological nervous system. Fig. 3 shows a nerve impulse recorded from an axon within the spinal cord. Its generation depends on the presence of small molecular batteries, which are termed "sodium channels." The important point here is that these channels, located within the nerve membrane, are essential for the transmission of messages within the nervous system. The presence of these channels is one of the characteristics that differentiates nerve cells from other types of cells, and they must be replaced following injury, if the nervous system is to recover normal (or even close-to-normal) function.

Fig. 4 shows the membrane of a nerve fiber, magnified hundreds of thousands of times through the electron microscope. The available data suggests that the particles within the membrane represent the sodium channels. Thus, the molecular underpinnings of neuronal activity can now be visualized. Moreover, much is now known about how these channels function, and how they gate electrical currents. Researchers will soon be able to isolate these channels and determine their detailed structure. An important question is, how are they synthesized? How are they transported from their site of

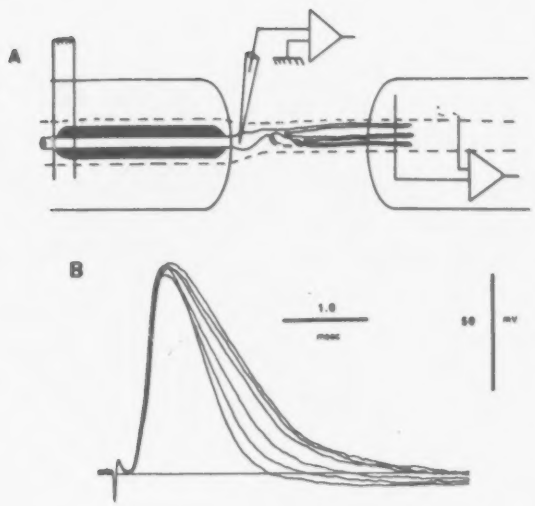
Figure 4.



synthesis (in the nerve cell body) to the axon, and what holds them in place? Can we understand and possibly encourage channel production in regenerating neurons? In order to do this, we must study them directly during regeneration.

Newly developed techniques, in fact, permit the detailed study of mechanisms of regeneration of nerve fibers. It is now possible to visualize, as in Fig. 4, the insertion of newly formed proteins into regenerating nerve cells. It is also possible, as shown in Fig. 5, to obtain electrical recordings from peripheral nerve fibers which have regenerated after injury. Here, one can monitor the electrical activity in regenerated nerve fibers. Notably, these regenerated fibers exhibit relatively normal functional

Figure 5.



properties. It is, moreover, possible to study the detailed sequence of events, at the cellular and molecular levels, by which regeneration occurs. It is possible, for example, to compare regeneration with normal development. There are significant parallels in these two sequences. There is every reason to think that, given modern research techniques, we will be able to understand this neural regeneration increasingly well.

It should also be pointed out that a number of research groups are developing drugs which modify, in a predictable way, the behavior of these channels, so that they generate more ionic current (the current underlying nerve signals). Fig. 5, in fact, shows the increase in current which is produced by one of these drugs. This increase in current following pharmacological treatment is necessary for conduction through damaged nerve fibers. This is an example of an approach, whereby it may be possible to develop effective symptomatic therapies for diseases such as multiple sclerosis and spinal cord injury.

In addition, there is considerable work being carried out on species in which regeneration of the central nervous system does occur. As one example there is Sternarchus, a fish which regenerates the spinal cord following spinal cord injury. Fig. 6 shows a normal spinal cord from this species.

Figure 6.

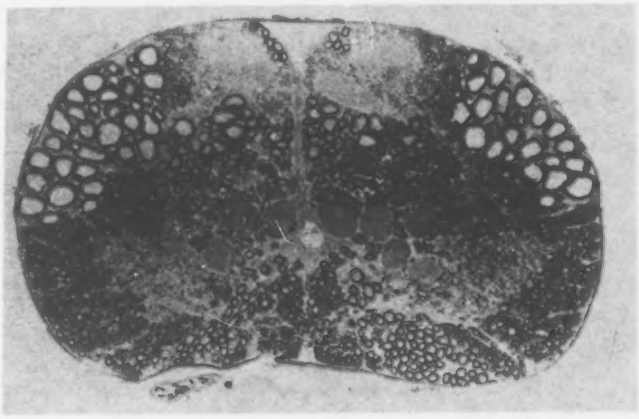
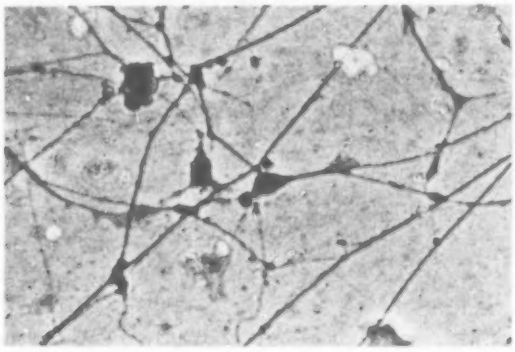


Figure 7.

Fig. 7 shows a spinal cord which has regenerated following injury. The regenerated cord recapitulates the normal structure. It also functions normally. The important point here is that, in species such as this, there is a striking regrowth of nerve cells following injury. Recently, it has become possible to isolate the progenitors of the regenerating nerve cells, and to maintain them in tissue culture (Fig. 8). It appears that we will soon understand details of the mechanisms by which new neurons are produced, and by which they grow and establish connections with each other.

Figure 8.



Obviously men are not fish. Nevertheless, it is highly likely that the basic principles of cell growth, discerned from such elementary systems, will turn out to be relevant to man. Work carried out at a variety of levels, from elementary (but experimentally tractable) model systems to man, will be necessary in this research effort.

Despite the progress outlined above, there are a number of very important questions which remain, with respect to the ways in which the nervous system responds to injury. These include:

What are the mechanisms by which newly formed nerve cells differentiate?

What signals turn on (and off) nerve cell growth?

What guides nerve fibers to their correct target?

Do glial scars prevent the regrowth of nerve fibers through the damaged central nervous system?

How do nerve cells produce the proper connections with their targets?

How can regenerative processes be promoted following injury to the nervous system of mammals, including man?

In disorders such as spinal cord injury, it may not be necessary to achieve total structural regeneration following the insult. The important goal is functional recovery. We know, from the example of multiple sclerosis, that functional recovery can occur in man, as a result of subtle changes at the cellular and subcellular levels following injury to the central nervous system. We also know, from laboratory experiments, that a degree of regeneration can occur following central nervous system injury under some circumstances, and that regeneration can be altered by a number of experimental manipulations.

If we can encourage regeneration of even several percent of the fibers in patients with spinal cord injury, I believe these patients will put those regenerated fibers to good use. Even the development of a partial gait would be a marked advance for the spinal cord injured patient. The time is ripe for further work in this area, and it is highly likely that there will be significant progress over the next few years.

This concludes my statement. I would be pleased to answer any questions that you or members of the Committee may have.

RESEARCH FOR A POSSIBLE CURE FOR PARAPLEGIA

STATEMENT BY DR. JERALD J. BERNSTEIN

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VETERANS ADMINISTRATION MEDICAL CENTER
WASHINGTON, D.C.
AND
PROFESSOR OF NEUROSURGERY AND PHYSIOLOGY
THE GEORGE WASHINGTON UNIVERSITY SCHOOL OF MEDICINE
WASHINGTON, D.C.

PRESENTED BEFORE

SUBCOMMITTEE ON HOSPITALS AND HEALTH CARE
COMMITTEE ON VETERANS' AFFAIRS
HOUSE OF REPRESENTATIVES

APRIL 26, 1984

INTRODUCTION

I am Jerald J. Bernstein, Ph.D.--a basic neuroscientist and the Chief of a Veterans Administration basic science laboratory dedicated to researching mechanisms to regrow the spinal cord after injury. I am also a Professor of Neurosurgery and Physiology at the George Washington University School of Medicine. Both of these institutions are in Washington, D.C. I have been engaged in spinal cord regrowth research for 25 years and I am the author of over 125 papers on the subject. I am testifying as an expert in the field of spinal cord regrowth after injury.

There are approximately 500,000 para- and quadriplegics in the United States today. Paraplegics are confined to wheel chairs and quadriplegics are bed ridden for the duration of their lives. As a result of modern medical techniques para-and quadriplegics are in this condition for a period of an average of 38 years after injury. The physical deterioration resulting from spinal cord injury claims approximately 20,000 victims each year. It occurrs primarily in young males 16-25 years of age. The main causes of para- and quadriplegia are the automobile, work, and sport related injuries. The cost of medical care for these patients has been estimated at $1,000,000 per patient.

Because of age, the young men and women in the military fall in the prime risk group for domestic accidents that cause paraplegia. In times of war, when citizens protect our way of life, the number of patients with this disease increase dramatically. Spinal cord injury centers in the Veterans Administration Hospitals supply patient care and rehabilitation for these patients; however, it was necessary to initiate a basic science research program to develop a cure for this debilitating disease in order to return para- and quadraplegic people to more active and productive lives.

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In 1980 I was recruited into this program by the Veterans Administration to establish a laboratory which would undertake the development of a basic research program to identify areas of research for an eventual cure for para-and quadriplegia. Basic science is the only approach to find a cure for this disease that effects so many people and is so costly to our society.

PARA- AND QUADRIPLEGIA

Spinal cord injury in para- or quadriplegia results in a disconnection of the spinal cord from the brain. The body below the injury has no sensation or controlled muscle movement. In addition, there is often pain of unknown origin, the muscle below the injury waste away, and many other problems ensue. The nerve fibers that connect the spinal cord and brain after the injury are either mechanically damaged or cease to transfer information across the area of injury. To date research has not led to solution of the problem of the inability of the damaged nerve cells to regrow across the site of injury.

Humans and other mammals have their total complement of nerve cells and nerve fiber processes (which connect the nerve cells of the brain with those in the spinal cord) in early infancy. Shortly after birth no new nerve cells are produced. Our laboratory has undertaken a series of experiments in lower mammals with the goal of establishing a method of supplying new, growing, and active nerve cells to a damaged adult spinal cord of a paraplegic. We have initiated experiments in the first nervous system spinal cord transplants in an animal model. The objectives of these experiments are to determine: 1) if a transplant of new nerve cells can be introduced into an adult injured spinal cord; 2) if the newly transplanted nerve cells survive; 3) if the transplant will allow the regrowth of nerve fibers from the animals with the injured spinal cord; 4) if new connections to and from the transplant can be formed and reestablish functional connections between the brain and spinal cord below the area of the injury.

RESEARCH

The first diagram is a representation of the normal spinal cord. This miraculous structure contains nerve fibers on the outside of the spinal cord which transfer information from the brain to the body through the spinal cord and from the body through the spinal cord to the brain. This information includes sensation from the body, most of which you are unaware of until asked to think them. Are my socks tight? Did I wear that pair of shoes with the strap that always rubs my toe? Is my leg in that position I always place it when sitting at my desk; which always shortens my leg muscles and makes me limp when I get up?

It is inherent in these question that there is not only information of body sensation and position transfered to your brain but also information is coming from your brain going to your body. In the case just mentioned about your leg muscles, for example, how did your leg muscles shorten? It is by means of a brain transmitted message. This information is passed in the nerve fibers in the outer spinal cord as seen in the first diagram. The information is gathered in the body and sent by nerve fibers into the top aspects of the spinal cord and the muscle movement information is passed to the body from the lower aspects of the spinal cord. These transfers are accomplished by nerve cell circuits connecting spinal cord and brain through many nerve cells each of which are found inside the spinal cord (represented in the diagram of the spinal cord by the central butterfly shaped structure) and brain all contributing information. The diagram now in front of you represents the spinal cord in the upper body in the illustration on the top and the spinal cord in the lower body in the illustration on the bottom.

The diagram on the next page (2) shows the consequences of a spinal cord injury which results in paraplegia. Paraplagia can be a result of brusing the spinal cord from a radical snapping back of the head on the neck, for example, in severe whiplash when your car is struck from behind while your

car is not in motion. This causes a mechanical or functional disconnection of the spinal cord and the disconnection of the body below the injury from the brain, followed by the loss of sensation and movement from the body below the injury.

We are now presently faced with a permanent injury in which we cannot replace the nerve cells, because as mentioned earlier, mammals, such as we all are, do not produce nerve cells after infancy. Since we do not produce new nerve cells, we do not produce new nerve cell-nerve fiber circuits. Again, due to the fact that we cannot replace the lost nerve cells and nerve fibers, we are now confined to a wheel chair for the rest of our lives.

Our experimental attack on the problem is to provide a source of new nerve cells which we will study for there survival, growth, ability to produce new nerve cells, nerve cell connections and circuits as was accomplished when our injured adult was first developing. For this reason we chose to use the developing rat brain and spinal cord, which are doing all of these things normally, and place it in the spinal cord of an adult rat with a spinal cord injury, as seen in the illustration. It must be remembered that a spinal cord injured rat also looses sensation and muscle movement below the site of injury. The piece of developing brain or spinal cord is placed in the spinal cord with a needle as seen in illustration 3.

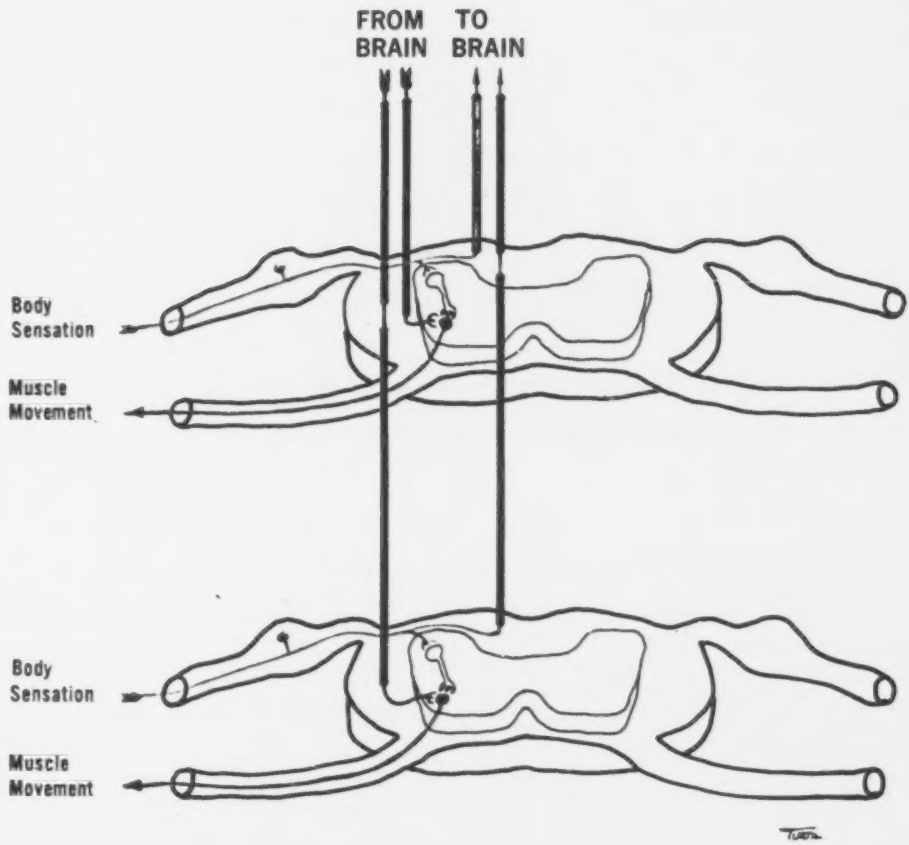
I can tell you that the developing tissue survives, grows by adding new nerve cells, because it retains its normal ability to make new nerve cells, and lives the duration of the experiment, which was 6 months. We have accomplished and are on the forefront of the first spinal cord transplants in experimental animals. Even for me this feels like science fiction. We are now studying spinal cord transplants as in the earlier stages of liver and heart transplants, which we now accept as routine.

The next figure (4) demonstrates what the expectations of this research are for the future in clinical applications. I would like to stress that these experiments are still in the developmental stages. It would be unpardonable of me to give false hope to the many victims of paraplegia. With these caveats let us look at the expectations of this research. In the fourth diagram, the transplant has now grown to fill the injury in the spinal cord. New nerve cell fibers have grown from/and to the transplant connecting the injured spinal cord with the transplant and vice versa. This process is aided by the formation of new nervous system circuits within the transplant. The injury site would be bridged--restoring the sensation and motor movement.

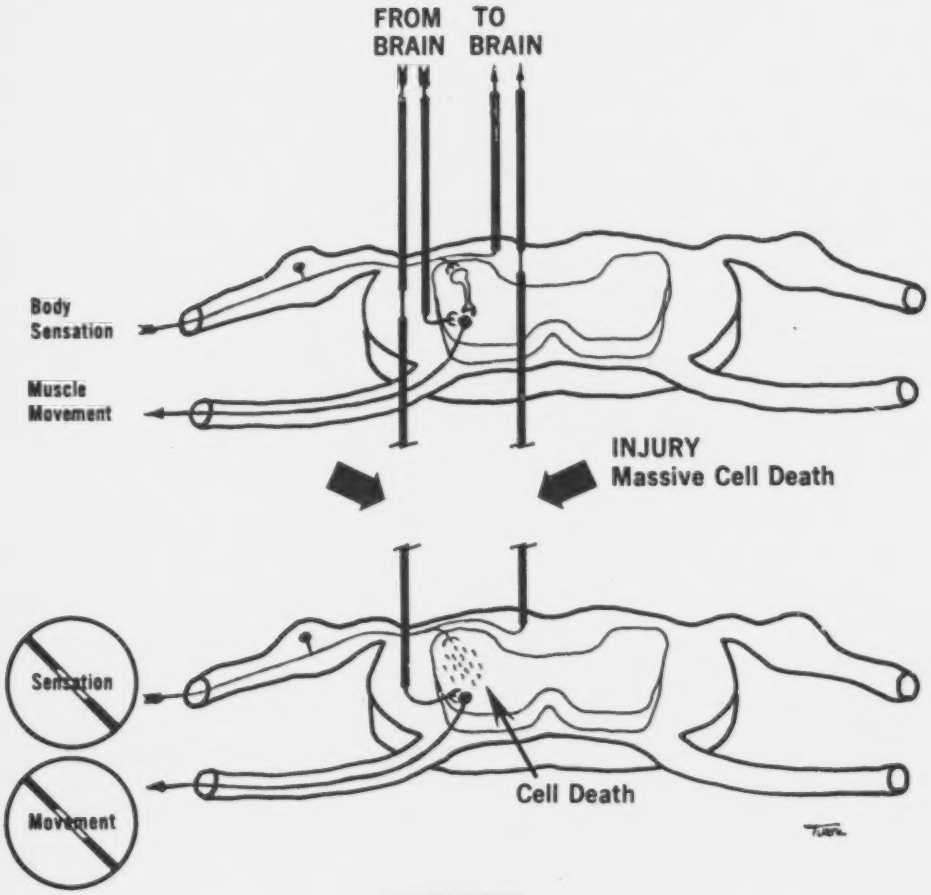
The next diagram has an overlay and is the outline of an underlying photograph taken through a microscope. If you will look at the top middle portion of the overlay it normally would contain only nerve fibers connecting the brain and spinal cord. If you turn up the overlay you will see an adult animal spinal cord with a developing transplant growing where only nerve fibers grew previously. The transplant is outlined on the overlay. This transplant contains new nerve cells and new nerve fibers.

We must now determine if the adult spinal cord and the transplant will form connections between them. Will these connections be functional? Most importantly, will these transplants reverse the tragedy of paraplegia? The work must continue or we will never know the answers.

That concludes my statement, Mr. Chairman. I will be pleased to answer any questions you or members of the committee may have.

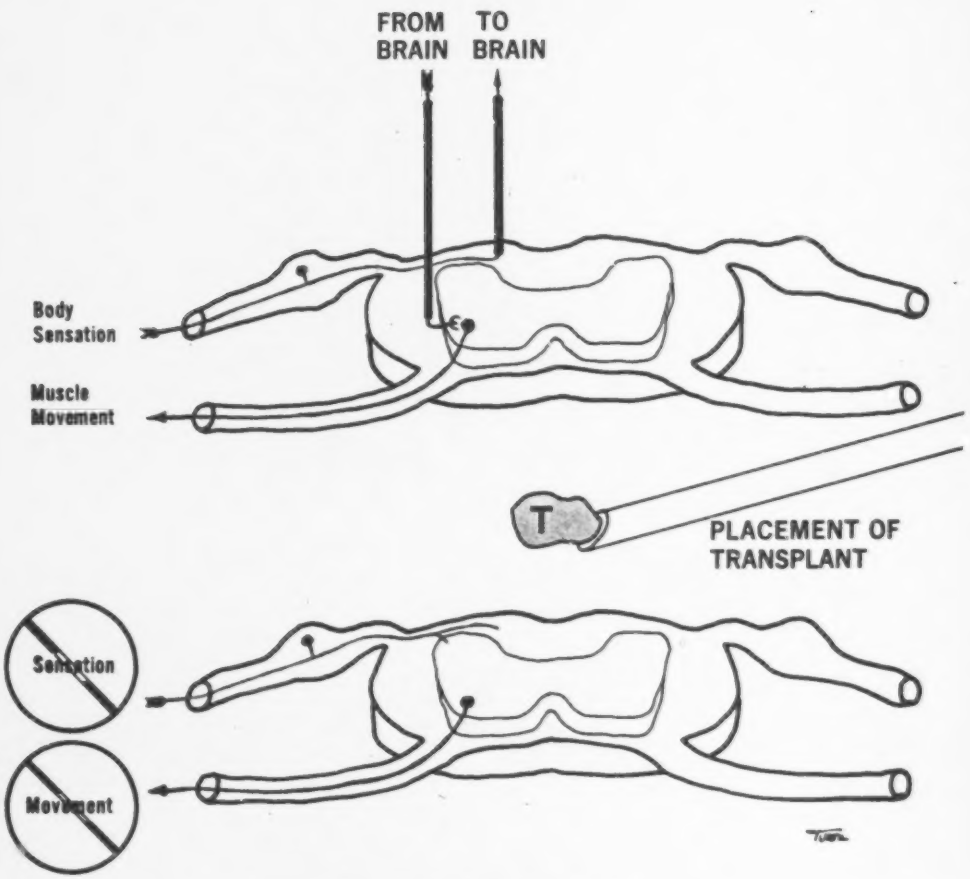


NORMAL SPINAL CORD


FROM BRAIN
TO BRAIN
Body Sensation
Muscle Movement
INJURY
Massive Cell Death
Sensation
Movement
Cell Death

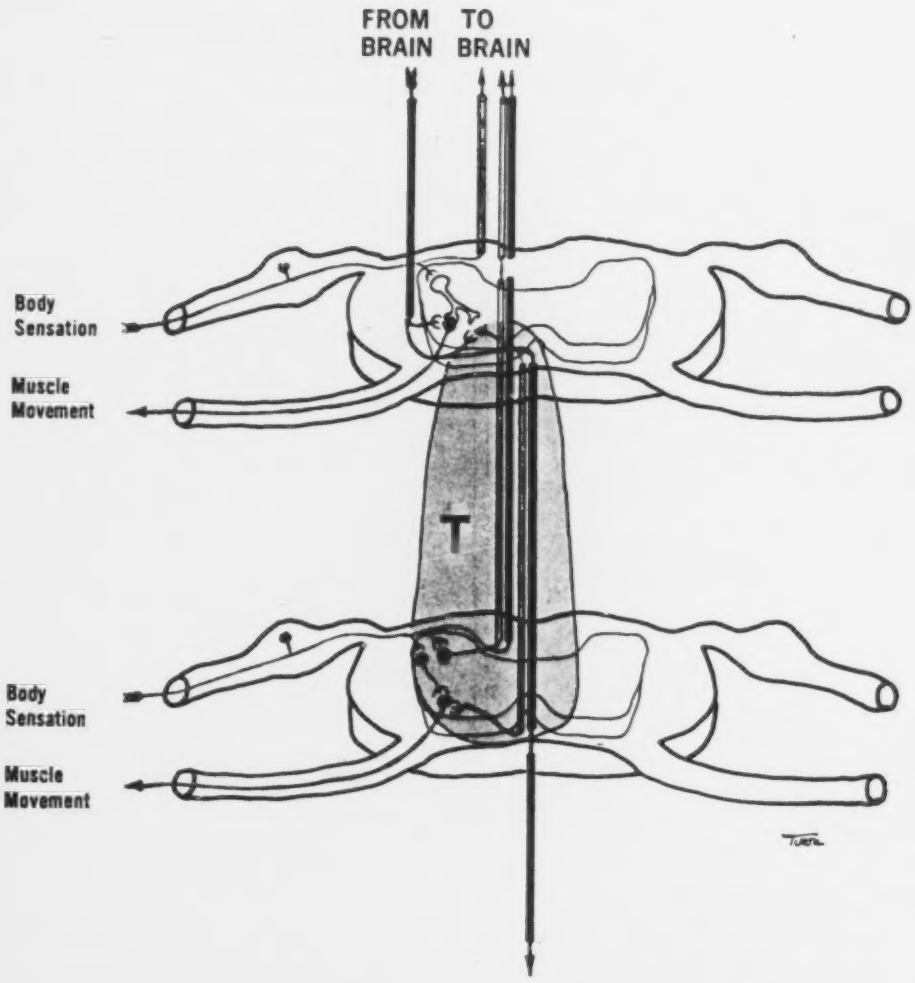
INJURY

②



TRANSPLANTATION

③



RESEARCH GOAL FOR PARAPLEGICS ④

STATEMENT OF

FREDRICK J. SEIL, M.D.

DIRECTOR, VETERANS ADMINISTRATION OFFICE OF

REGENERATION RESEARCH PROGRAMS

BEFORE THE

SUBCOMMITTEE ON HOSPITALS AND HEALTH CARE

COMMITTEE ON VETERANS AFFAIRS

HOUSE OF REPRESENTATIVES

April 26, 1984

Mr. Chairman and Members of the Committee:

Thank you for this opportunity to testify before you today about some facets of the Veterans Administration program of regeneration research as related to the nervous system.

My name is Dr. Fredrick Seil. I am a medical doctor and I am the Director of the Veterans Administration Office of Regeneration Research Programs, which was established in 1981. The Office is located at the VA Medical Center in Portland, Oregon. I would like to tell you briefly about some of the functions of the office.

We have, among other things, sought to increase communication between scientists involved in various aspects of regeneration research, and to that end have established a newsletter that is mailed to scientists all over the

world. Results of conferences and symposia are reported in this newsletter, and guest articles by leading investigators address current issues in regeneration research. The newsletter also provides a format in which scientists may address controversial issues and report negative results. The newsletter is not restricted to VA investigators, but seeks to link VA scientists with scientists around the world whose common interest is regeneration research.

Another activity of the office to improve communication among scientists has been the organization of VA sponsored symposia. To date, three such symposia have taken place, including one last month (March, 1984) on the neurochemistry of regeneration, held in conjunction with the annual meeting of the American Society for Neurochemistry. A VA sponsored symposium held in Harpers Ferry in September, 1982, resulted in the publication of a state-of-the-art book entitled, "Nerve, Organ, and Tissue Regeneration: Research Perspectives," which was published last year (1983). Another major symposium is planned for 1985, which will include scientists from this country and from overseas, and publication of another book on the latest developments in regeneration research is planned consequent to this symposium. These symposia, like the newsletter, have not been restricted to VA investigators, but have sought to increase communication between all scientists in the field.

These are some aspects of what the VA Office of Regeneration Research Programs does. I would now like to go on and tell you about some other kinds of research related to nervous system regeneration that are in progress, in addition to what you have already heard from Drs. Waxman and Bernstein.

One promising area for the regrowth of severed peripheral nerves is the use of plastic tubing to provide a channel for regrowth. When a peripheral nerve is cut, the ends usually retract from each other, leaving a gap. Two VA supported investigators, Drs. Betty Uzman in Memphis and Richard Sidman in Boston, are investigating the use of various kinds of plastic tubes to promote growth of nerve fibers from one cut end of the nerve to the other. I have here an example of the kind of tubing that Dr. Uzman is using in her experiments with mice, and the first slide (Fig. 1) illustrates how this tubing is used to provide a conduit between the severed nerve stumps.

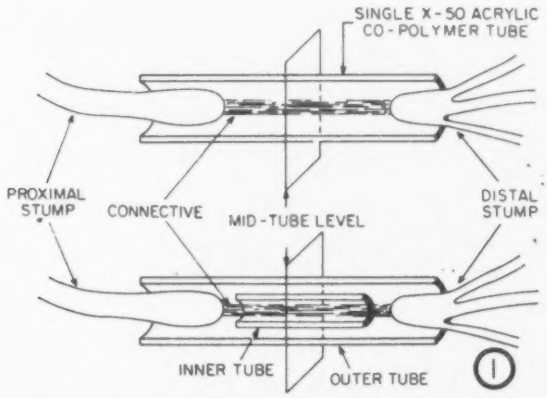


Fig. 1. Mouse sciatic nerve regenerated through semi-permeable tubes: diagram of experimental paradigms. (From ref. 8, with permission from Alan R. Liss, Inc.)

Dr. Sidman has used this technique with the optic nerve, the nerve from the eye to the brain, and has found regrowth of optic nerve tissue in such plastic channels. The ultimate hope is that if this system works with peripheral and optic nerves, perhaps the technique may someday be used to regenerate more complex systems such as the spinal cord.

Another area of research in nervous system regeneration that shows great promise is the study of factors that promote the survival and growth of nerve cells. Dr. Rita Levi-Montalcini and her co-workers in St. Louis described the properties of one of these, called nerve growth factor, over 30 years ago. This protein factor was found to be essential for the survival of certain types of nerve cells, or neurons. Nerve growth factor also caused a tremendous growth of nerve fibers from certain other neurons during some stages of development. This is shown in the second slide (Fig. 2), which compares the outgrowth of fibers from a group of sensory neurons without (top) and with (bottom) presence of the nerve growth factor protein. Since this early work, other growth factors have been discovered, and the list is growing longer. It appears that there may be specific growth factors for each of the thousands of different types of neurons within the nervous system. There are even separate growth factors for the supporting cells of the nervous system, the glia. Some of these factors may also function to guide nerve fibers to their appropriate targets, so that proper connections are made with other nerve cells, or with muscles or whatever structures the nerve fibers innervate. These growth factors may appear in some animals during development, when there is a great deal of elaboration of nerve cell processes. The problem with regard to regeneration is that once development of the nervous system is complete, some of these growth factors may disappear. They may therefore not be available when needed to promote nerve regeneration after an injury or some other insult. Thus it becomes very important to identify and characterize these growth factors, as it is conceivable that such factors may need to be provided for successful regeneration to occur. One of the possible differences between the inability of higher animals to regenerate certain parts of the central nervous system,

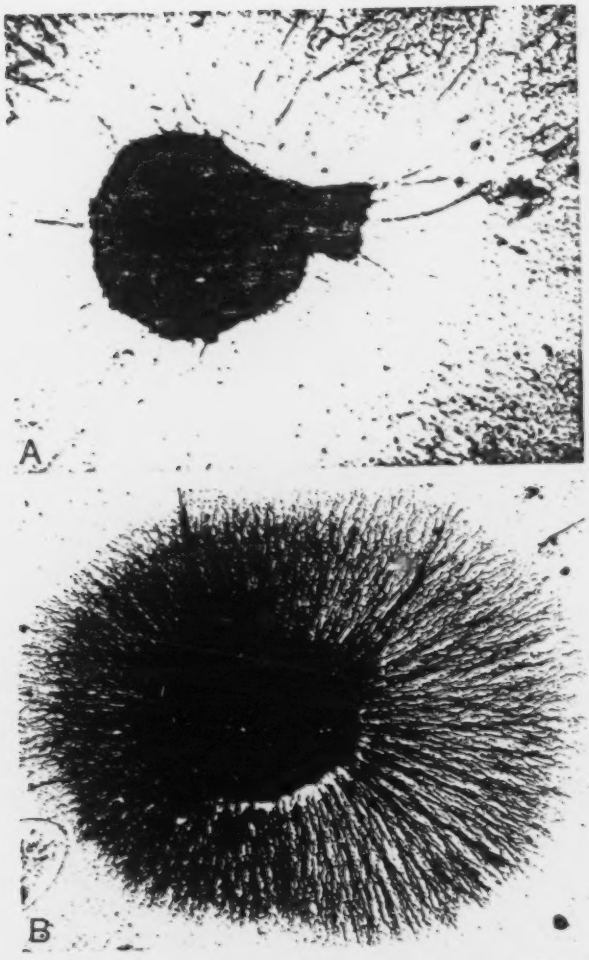


Figure 2. Photomicrographs of sensory ganglia of a 7-day chick embryo cultured in a control medium (A) and in the same medium supplemented with nerve growth factor (0.01 μg/ml) for 24 hr (B). Silver impregnation. From R. Levi-Montalcini, *Science 143*: 105–110 (1964), copyright American Association for the Advancement of Science.

such as spinal cord, and the regenerative capabilities of some lower animals, such as the Stenarchus described by Dr. Waxman, is that the lower animals are able to form new nerve cells throughout their adult lives. Therefore the various growth factors may always be present in these lower forms. Such factors may, however, have to be provided artificially in higher animals to promote nervous system regeneration. This is an extremely important area of research, and a number of laboratories, both within and without the VA system, are devoted to this problem.

A final type of research that I would like to illustrate is based on an example from my own laboratory. We are able to grow nerve cells in glass chambers, such as the one I have here. With these simple tissue culture models that can be observed in the living state with a microscope, we can put together fragments from various parts of the nervous system to learn some of the rules by which they interact. We can also take a certain population of nerve cells that consists of several different types of nerve cells that are highly interconnected, eliminate one of the cell types by exposing the culture to a drug that is toxic to only that type of neuron, and see what kinds of new connections are made by the remaining neurons to compensate for the missing elements. Once this has been established, we can then reinsert the missing cell type from another source to see if there is a second reorganization that culminates in restoration of an approximately normal state. This simple model system approximates the way a nervous system transplant might work, and gives us some clues as to priority rules nerve cells have for making connections with each other. This is a very important issue in regeneration research, as the right connections must be made if a regenerated nervous system is to function properly. It thus behooves us to

learn the rules by which these connections are established.

If you ask me where I think regeneration research is going, I will say that you are going to see many more experiments of the type that Drs. Waxman, Bernstein and I have talked about. I think especially that you are going to see remarkable developments in the areas of nerve transplantation and a greater understanding about the role of nerve growth factors. I think that there will be continued steady progress in learning more about how the nervous system develops, which is essential to understanding regeneration. Breakthroughs in the field of molecular neurobiology may allow research developments that we cannot even conceive of at the present time.

Progress in regeneration research has been made. Only 15 or 20 years ago it was widely held that regeneration in the central nervous system of higher animals was not possible. This view has already been disproved since at least partial central nervous system regeneration has been shown under a variety of conditions. A great many things need to be learned before we can think in terms of practical applications for man, but this is a relatively young field, and a real acceleration of research development in regeneration is just beginning. No one is in a position to predict when or how soon the breakthroughs will happen, but we have every reason to believe that significant progress will continue, and that ultimately our hopes for using the fruits of this research to benefit mankind will be realized.

That concludes my statement, Mr. Chairman. I will be happy to answer any questions you or members of the committee may have.

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Department of
Medicine and Surgery

810 Vermont Ave., N.W.
Washington, D.C. 20420

Veterans
Administration

IL 15-84-3, March 1984

NEWSLETTER

Regeneration Research

Spinal Cord Injury Research
Persepective of a Consumer Organization

Lynn Phillips, *National Research Director*
Paralyzed Veterans of America
Washington, D.C.

If there is one question I hear more often than any other, it is, "How close are we to finding a cure for spinal cord injury?" To many individuals with spinal cord injuries, the thread of hope that there someday might be a cure gives them the impetus to find a way to cope with life after injury.

I presently serve as National Research Director for the Paralyzed Veterans of America (PVA). What I would like to do in this article is to acquaint the neuroscience community with this somewhat unique organization, and describe PVA's efforts to support research in fields related to spinal cord injury.

The PVA was started in 1946 by spinal cord injured veterans in military and VA hospitals throughout the country. Each of these initial groups, the forerunners to PVA's local chapters, faced questions that literally had not been faced by any other group of human beings before, since prior to World War II virtually everyone who suffered a spinal cord injury died from his injury or related complications within months after sustaining injury. What was "life after injury" like? Could we work? Go back to school? Get married? Have sex? What do we do about getting into and out of buildings? How long will we live?

The response to these questions was varied. Some well-meaning staff people at the VA hospitals did their best to make the hospital a "home away from home," with the assumption that these veterans would be dying soon. Others seemed to realize that some sort of rehabilitation program should be started, and so began to develop such programs. But the most impressive actors in this scenario were the spinal cord injured veterans themselves. From the very beginning they took an active role in determining their own futures. One of the things they did was to organize themselves into Paralyzed Veterans Associations at their local hospitals and in communities surrounding those hospitals. In 1947, delegates from seven of these local organizations met in Hines, Illinois to form a new national organization, the Paralyzed Veterans Associations of America. Since that time, PVA has played an active role in obtaining improved benefits and services for veterans and disabled persons.

Today, PVA has 33 chapters and approximately 11,000 members. As a congressionally chartered veterans' service organization, PVA's foremost mission is to provide service to veterans, particularly in the areas of securing VA benefits to which they are entitled. The PVA also plays an active role in advocating improvements to federal programs for veterans and disabled individuals through its legislative and advocacy programs. And, throughout its history, one of PVA's major goals has been to promote research that will lead to better care for spinal cord injured individuals and ultimately to a cure for this condition.

In 1976, PVA formalized its research support by establishing the PVA Technology and Research Foundation (TRF). To date, TRF has awarded over $2.5 million to researchers in fields related to spinal cord injury, with approximately one-half of that total going to neuroscience research. Inquiries about application procedures and the kinds of research projects that

have been supported in the past can be addressed to TRF, Paralyzed Veterans of America, 801 Eighteenth Street, N.W., Washington, D.C. 20006.

The TRF has two funding cycles per year. Deadlines for receipt of proposals are January 1 and July 1, with decisions being made the first weekend of May and November, respectively. All proposals undergo a preliminary review by our Scientific Advisory Board (Stephen Waxman, M.D., Ph. D. and James Albers, M.D., Ph. D. are the current neuroscience representatives on the Scientific Advisory Board) and then are sent out for peer review to 3-5 reviewers. All funding decisions are made by the TRF Board of Trustees, which is composed of seven PVA members who have expertise in one or more areas of spinal cord injury research.

The size of grants given by TRF is considerably smaller than those given by federal agencies, but can play an important role in the larger research picture. The average size of a grant is in the $25,000-$30,000 range annually, and grants can be renewed up to a total of three years. The TRF is a particularly good funding source for pilot project funding or for postdoctoral research fellowships. In fact, several researchers who received "start-up" funds from TRF now are established researchers in their fields.

Spinal cord injury is a complex problem to address. No single group of persons - physicians, neuroscientists, consumer groups, or engineers - can address all of the aspects of this problem adequately. If we all continue to do our own parts with total dedication and hard work, perhaps someday this problem can be alleviated.

Skeletal Muscle Regeneration and Transplantation

Bruce M. Carlson, M.D., Ph.D.
Departments of Anatomy and Biological Sciences
University of Michigan
Ann Arbor, Michigan

The history of research on skeletal muscle regeneration reflects strikingly the manner in which prevailing attitudes in science and medicine can influence the development of a field of science. Muscle regeneration was first documented by pathologists nearly a century ago. These early histological descriptions of muscle fiber breakdown and repair were very accurate, but they failed to excite the imagination of the biological and medical scientists of the day. In the early 1900's statements that skeletal muscle does not regenerate crept into the pathology and surgery textbooks, and for many decades thereafter skeletal muscle regeneration in mammals was not seriously considered as an object for either scientific research or clinical application.

Things began to change during World War II when Le Gros Clark, working as part of an English project on the repair of war-related injuries, wrote a series of papers on the regeneration of rabbit muscles after ischemic injury. Numerous studies on the reinnervation of muscle were carried out as part of the same effort.

Shortly after the war the scene shifted to Russia, during the peak of the Lysenko era. Under the influence of Lysenko and his disciples, much of Soviet biology underwent a great upheaval, during which classical genetics was virtually eliminated as a science and replaced by other concepts. The influence of the environment upon biological processes was strongly stressed. A curious doctrine of the times was Lepeshinskaya's "new cell theory", which stated that under some circumstances, such as traumatic injury, new cells do not need to arise from pre-existing cells; rather, they could arise *de novo* from a proteinacious "living substance." It was during this era that Studitsky (1959) first reported that an entire mammalian skeletal muscle could regenerate after it had been minced into small (one mm^3) fragments, and the fragments were replaced into the bed of the removed muscle. At first this experiment was interpreted as demonstrating the validity of the new cell theory, because it was assumed that the original muscle cells died as the result of mincing, and it was concluded that the new muscle cells arose from "living substance." Regardless of their original interpretation, the Russian experiments demonstrated that the massive regeneration of skeletal muscle is possible under certain conditions. This emphasis on "conditions" (i.e. environmental effects) has proven to be a very important factor in conducting experiments on the regeneration of a wide variety of mammalian tissues and organs.

During the 1950's muscle regeneration was still little recognized outside the Soviet Union. Lack of experience in this area showed up clearly in the toxicity testing of some of the newer local anesthetics, which were being developed at this time. It is now well established that most of the commonly used local anesthetics are highly myotoxic in laboratory animals. Original toxicity tests were often interpreted as showing "some muscle atrophy", whereas in reality the investigations show general evidence of regeneration rather than atrophic muscle fibers.

The next important step in the development of muscle regeneration research was the discovery of the satellite cell by Mauro in 1961. The satellite cell is an unspecialized mononuclear cell that lies between muscle fiber and its overlying basal lamina. The suggestion that the satellite cell might serve as a precursor of regenerating muscle cells sparked a lively controversy about the cellular origins of regenerating muscle. The major debate, well summarized in a symposium report (Mauro *et al.*, 1970), revolved about whether the myonucleus or the satellite cell serves as the myogenic cell in

regeneration. Several years later, the satellite cell was shown to be a source of myoblasts in mammalian muscle regeneration, but other possible cellular sources have still not been definitively ruled in or out (see symposium report by Mauro *et al.*, 1979).

During the same period, biologically oriented studies showed that there were some fundamental differences in mechanisms between the regeneration of entire muscles (mammalian and amphibian) in otherwise uninjured limbs and the regeneration of entire muscles in the context of a regenerating limb (Carlson, 1972, 1979). In a regenerating limb many aspects of muscle regeneration recapitulate the embryonic development of muscles. Here, muscle formation is an integral part of the development or regeneration of the limb as a whole, and cannot be separated from it. In contrast, the regeneration of an isolated muscle within a limb relies heavily upon 1) a local source of myogenic cells, 2) an appropriate mechanical environment and 3) reintegration of the regenerating muscle tissue with the vascular and nervous systems of the host.

A major breakthrough in the clinical application of muscle regeneration came in 1971 when Thompson, an English plastic surgeon, reported the first successful cases of free muscle grafting in man (Thompson, 1974). (In standard muscle grafts, a muscle is completely removed from its bed, with the tendons, nerves and blood vessels severed. Upon reimplantation into a suitable bed, the muscle is sutured to fixed sites at either end; the graft relies upon spontaneous revascularization and reinnervation.) Thompson did not believe that skeletal muscle can regenerate and interpreted the success of his operations on the basis of manipulations designed to enhance the survival of muscle fibers. Subsequent laboratory research has shown, however, that the degeneration and subsequent regeneration of muscle fibers is a major mechanism in the successful establishment of a free muscle graft.

Early clinical applications of free muscle grafting were directed toward alleviating the symptoms of unilateral facial palsies and anal sphincter incompetence. Both laboratory studies and clinical applications of free muscle grafting have been hindered by considerable variability from one graft to the next and a relatively low (less than 50%) return of original functional mass.

Typically, only small muscles (under 6 gm) can be freely grafted with constant success. These limitations are acceptable for grafts in which great strength is not required, but free muscle grafts are not appropriate for muscles in which the generation of large amounts of tension is required. In recent years, microsurgical techniques, involving microsurgical anastomoses of both nerves and blood vessels, have been applied to many muscle grafting procedures. Many of the recent clinical applications of muscle grafting are summarized by Freilinger *et al.* (1981).

Recently, several laboratories have discovered that it is possible to "seed" muscle fibers with exogenous myogenic cells (Sloper and Partridge, 1980; Jones, 1979; Lipton and Schultz, 1979). With this technique, myogenic cells injected into a muscle migrate beneath the basal laminae of existing muscle fibers and fuse with the muscle fiber. It has been proposed that certain muscle diseases (e.g. dystrophies) might be treatable by seeding normal myoblastic cells into dystrophic muscles.

Another major area of current research activity involves the reinnervation of regenerating and transplanted muscles. In some systems (Rubin and McMahan, 1982) the persisting basal lamina in the motor endplate region has been shown to be very important in the reestablishment of neuromuscular connections in regenerating muscle, but recent evidence suggests that reinnervation is controlled by a greater variety of mechanisms than was originally anticipated.

Many problems remain to be solved in muscle regeneration and transplantation, from the standpoint of both the basic science and clinical application. Some of the major ones are listed below.

1. How does formerly ischemic muscle regenerate - through the survival of local myogenic cells or by "seeding" from damaged, but viable muscle fibers?
2. To what extent does regeneration recapitulate ontogeny with respect to the sequence of isoforms of contractile proteins that appear during the course of regeneration?
3. What are the mechanisms involved in the reintegration of a regenerating or transplanted muscle with the neural and vascular systems of the host?
4. How can one reduce the variability and improve the functional mass of free muscle transplants?
5. Under what circumstances is it appropriate to use free muscle grafts clinically, and when should vascular anastomoses be applied?
6. How can physical training be employed in facilitating the functional recovery of muscle grafts?
7. What are the mechanisms of structural and functional recovery of vascular-anastomosed muscle grafts? This is turning out to be a much more complex problem than was originally anticipated.

Many of the above questions are under active investigation by a group of ten laboratories which are involved in interdisciplinary studies of muscle regeneration and transplantation at the University of Michigan, but muscle damage is so widespread (e.g. in athletic and military injuries, as well as disease processes) that investigators with a diversity of backgrounds and specific interests are becoming interested in muscle regeneration. A key factor in the current revival of interest in muscle regeneration is the recognition that skeletal muscle is not only frequently injured but that it is also more capable of extensive repair than was formerly supposed.

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Fourth Biennial Forum on Regeneration

Charles E. Dinsmore, Ph.D.
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The Fourth Biennial Forum on Regeneration was held at the University of Illinois in Urbana, June 2-4, 1983, with Drs. David L. Stocum (University of Illinois, Urbana) and Charles E. Dinsmore (Rush Medical College, Chicago) as co-hosts. A wide range of research interests was represented among the approximately 80 attendees with 32 investigators presenting some of their recent findings. Topics covered included everything from acquisition of regenerative potential during the development of tentacles in pluteus (sea urchin) larvae (Dr. Dale Bonar, University of Maryland) to the bilateral response to unilateral trauma in deer antler regeneration (Dr. George Bubenik, University of Guelph).

The regenerating urodele limb continues to be the dominant model at the Forum with new information being provided from several different laboratories and perspectives. Using three dimensional computer analysis of serially sectioned and staged regeneration blastemas, Dr. Thomas Connelly (University of Michigan, Ann Arbor) has found a correlation between growth, as measured by cell density and mitotic activity, and morphogenesis. Branch points, which can be identified in these parameters by computing a medial axis transform, predict or are indicative of major morphogenetic events such as digit formation.

Several investigators have returned to the use of nucleolar markers to address contemporary questions or reexamine earlier studies in light of our current understanding of regenerative processes. By transplanting distal limb tissues with nucleolar labels proximally, Dr. Christine Rollman-Dinsmore (University of California, Irvine) demonstrated that distal tissues can indeed participate in the regeneration of proximal structures. Using the same marker and staining techniques, Dr. Kenneth Muneoka (University of California, Irvine) demonstrated how graft contributions to induced, supernumerary limb regenerates could be readily identified and that the pigment marker in grafted skin is a poor marker relative to the genetic label. The triploid nucleolar marker was also described by Dr. Patrick Tank (University of Arkansas) who demonstrated that in the developing axolotl limb, a labeled posterior organizer grafted anterior to the limb field will induce supernumerary limbs which will contain labeled cells as well as host cells. A different mutant intranuclear marker has been used by Dr. Lois Patterson (University of Rhode Island) in her thesis work to show that cell contributions to the regeneration blastema on urodele limbs may arise from more proximal stump levels than has been previously assumed.

Another area of high activity and excitement involves the effect of retinoids on developing and regenerating limbs. Steven Thomas (University of Illinois, Urbana), working in Dr. David Stocum's laboratory, has worked out a dose- and time-dependent response to retinoic acid injected intraperitoneally into newts with regenerating limbs. Not only does the regimen produce serial reduplications of proximodistal structures, but he has also found anteroposterior and dorsoventral duplication as well in some cases. In another series of experiments on axolotls, he has shown that distal limb segments grafted into enucleated orbits are capable, when amputated and exposed to retinoic acid, of regenerating proximal as well as distal limb components. This is a highly significant finding with deep ramifications for our understanding of positional information and plasticity in pattern regulation.

Teratologists have known of the effects of retinoids on normal limb development for a long time and Dr. Thomas Kwasigroch (East Tennessee State University) provided an historical overview of these data as well as an analysis of his own work on quantitating the effects of retinoic acid using mammalian limb buds in organ culture. More detailed knowledge of how vitamin A and its derivatives modulate cellular interactions is currently being explored.

The heterogeneity of cells in urodele limb blastemas is being examined *in vitro* by Tim Hinterberger (University of Illinois, Urbana) in Dr. JoAnn Cameron's laboratory. Using myogenic potential as a criterion, differences have been found which relate to medium used, size of implant and level of amputation. Other *in vitro* studies of limb blastemas which were presented showed a localization of substance P (Dr. Morton Globus, Waterloo, Canada) which indicates a possible role for it as the mediator of neurotrophic effects in regeneration. Dr. Swani Vethamany-Globus (Waterloo, Canada) reviewed her work on the role of insulin in supporting limb blastemas *in vitro* and discussed recent findings which correlate high levels of endorphins with regenerative ability. Dr. Richard Liversage (University of Toronto) continued the analysis of *in vitro* systems by discussing his work on the effects of prolactin on newt tail regeneration and also reviewed the "hormonal milieu" concept. A model for investigating epidermal cell-substrate interactions using explanted whole newt limbs was described by Dr. Donald Donaldson (University of Tennessee). With this system, coverslips can be coated with test materials such as laminin or fibrinogen to determine the substrate's acceptability for epidermal migration and preliminary wound healing.

Anuran amphibians (frogs and toads) are generally incapable of limb regeneration and are therefore phylogenetically near-

neighbors of the urodeles. These species can be used to ask how regenerative ability may be artificially stimulated. Dr. Jerry Kollros (University of Iowa) has studied the period when metamorphosing tadpoles progressively lose their ability to regenerate their newly developed limb rudiments as they grow and mature. Having previously shown that amputation at early stages rescues the regenerative ability such that it is retained through developmental stages when it is normally lost, he now finds a scaling correlation between regenerate foot dimensions with repetitive amputation and total body length. In a repetition of and elaboration on the earlier work of Dr. Singer, Dr. Roy Tassava (Ohio State University) clearly showed that superinnervation of young bullfrog forelimbs can in some cases support postamputational morphogenesis. An interesting point was made when he showed that the deviated sciatic nerve can support outgrowth even when severed from its central cell bodies. Continuing this thought on the nature of neurotrophic factors in regeneration, Dr. Anthony Mescher (University of Indiana, Bloomington), whose earlier studies were concerned with similarities between nerve growth factor and myelin basic protein, discussed new findings that sciatin, a glycoprotein first extracted from chick sciatic nerve and which causes myoblast maturation in *in vitro*, has marked similarities to transferrin. His studies show that human transferrin and lactoferrin can both stimulate thymidine uptake in cultured newt limb blastemas with a specific requirement for the ferric form of iron. Sciatin may therefore be a transferrin analog, both structurally and functionally.

A final note on frogs in regeneration research was provided by Dr. Bruce Carlson (University of Michigan, Ann Arbor) who demonstrated that grafts of frog skin to axolotl limbs will support limb regeneration but that there is a graft age-related decline in this capacity. Skin from immature or juvenile frogs will support outgrowth in amputated axolotl limbs.

In addressing the problem of denervation effects on cell cycling, Dr. Cherie Olsen (Washington University, St. Louis) described a protocol which can deplete larval urodele limbs of neurotrophic factors. Subsequently amputated limbs show a significantly earlier arrest of cell cycling than limbs denervated at the time of amputation. This model should provide greater insight into the stage of the cell cycle at which denervated blastema cells are arrested.

The ultrastructure of urodele limb muscle during the 24 hours following amputation was discussed by Wendy Horbay (University of Toronto). Changes at and proximal to the level of amputation were described for both red and white muscle fibers.

Recent information from studies on arthropod limb regeneration serves as the base on which Dr. Jay Mittenthal (University of Illinois, Urbana) has developed a new model for morphogenetic information. In arthropods, which regulate according to both limb and segmental field patterns, positional values may be understood in terms of two or more physical quantities. These quantities may be represented as waves out of phase. This model has been used to explain the occurrence of experimentally induced variations in pattern during crayfish leg regeneration.

The so-called higher vertebrates are generally considered to be lacking in limb regeneration potential. However, Dr. Betty Sisken (University of Kentucky) presented some of her work showing that grafts of embryonic central nervous tissue into amputated limbs of three week old rats can induce ectopic bone histogenesis, and that amputated limb buds in four day chick embryos can regulate completely when embryonic neural tube is grafted into the stump. Determination of the mechanisms invcIved in this induced regulation may provide useful insight into normal tissue interactions in development and regeneration.

In another area which has received much recent attention, Dr. Joe Vanable (Purdue University) presented some current data on endogenous electric fields in regenerating newt limbs. Experimental manipulations of the system with pharmacological blockade of ion channels or battery implants to increase or reduce flow show a definite correlation between regenerative capacity and stump electric potentials. A question of importance in these and related studies on mammals is whether current is associated with growth or complex patterning or both.

Another area of high interest, regeneration of the spinal cord, was addressed by Dr. Margaret Egar (Case-Western Reserve University) using axolotls with spinal cords sectioned in the thoracic region. Urodele amphibians are capable not only of spinal cord regeneration during tail replacement but can also reunite cranial and caudal segments of sectioned or resected thoracolumbar cord. Dr. Egar discussed the sequential cytological events in the spinal cord during regeneration of function.

The final series of presentations focused on muscle and neuromuscular relationships. During the progress of murine muscular dystrophy, degenerative events outstrip the diseased muscle's capacity to regenerate. Dr. Peter Law (University of Tennessee) presented evidence that implants of myogenic mesenchymal cells from normal embryonic limb buds improve both the structure and function of the host dystrophic mouse muscle.

Development of the levator ani muscle in male rats is androgen-dependent. In order to determine whether or not the regenerative capacity of this muscle is also androgen-dependent, Dr. Shahzad Mufti (Ohio University) gonadectomised animals prior to inducing muscle regeneration with crush lesions. Regenerative events appear independent of specific steroidal influence although long term survival may be somewhat affected.

Whole muscle graft survival is another subject with both fundamental and clinical research aspects. Rachael Must (University of Michigan, Ann Arbor) found that "muscular neurotization", that is the regrowth of nerves into their functional association with a muscle graft, depends upon extant paths in the graft which the regenerating nerves can use to access the muscle fibers.

In amputated and regenerating newt limbs, Dr. JoAnn Cameron (University of Illinois, Urbana) examined the cytology of myofibers and adjacent cells to determine whether dedifferentiation of myofibers or a satellite cell population is responsible for contributing cells to the blastema. While no satellite cells were found at any stage of the regenerative sequence, a new cell type which may be the perivascular cell described by earlier investigators was examined in detail. It is outside of the sarcolemma, has a basement lamina of its own and appears to have myoblastic potential, and thereby may provide myogenic cells to the blastema.

Two papers presented data on the regenerative capability of avian muscle spindles. To determine whether or not intrafusal

fibers regenerate by the same mechanism as extrafusal fibers. Dr. Robert Hikida (Ohio University) has studied denervation-stimulated degeneration and early regeneration in wing muscles. In concluding that intrafusal fibers have a different regenerative mechanism, he showed that, unlike mammalian spindle fibers, they appear not to undergo phagocytic breakdown. Dr. Jon Walro (Ohio University) discussed the plasticity of free muscle grafts in their capacity to form muscle spindles. The number of spindles is quite variable between different muscles but generally characteristic for a particular muscle. Free grafting a muscle with few spindles into the bed of a muscle which normally has many will apparently elicit the development of more spindles than normal for the graft muscle.

In a final paper dealing with neuromuscular relationships during regeneration of the rat soleus, Mark Womble (University of Michigan, Ann Arbor) demonstrated the persistance of non-innervated end plate clusters on myofibers for up to 60 days.

As the regenerating muscle is reinnervated in its graft bed, proximal extopic end plates may form *de novo* but the axons continue to grow toward and subsequently innervate the original endplate sites, which were referred to as "endplate-like receptor clusters" because of their continued affinity for fluorescently labeled bungarotoxin. Resolution of this dual innervation of individual myofibers remains to be more closely analyzed.

APA Colloquium On CNS Transplantation

Fredrick J. Seil, M.D.
Office of Regeneration Research Programs
VA Medical Center
Portland, Oregon

A colloquium entitled, "The Use of Embryonic Cell Transplantation for Correction of Central Nervous System Disorders," sponsored by the American Paralysis Association, was held at Pine Manor Junior College in Chestnut Hill, Massachusetts from June 27-29, 1983. The purpose of the colloquium was to review and discuss the use of embryonic cell transplantation in restoring function to central nervous systems damaged by injury, degenerative diseases, or other disabling conditions. The following is a summary of the major presentations of this colloquium.

Richard A. Murphy, M.D. of the Harvard Medical School initiated the proceedings with a review of some of the properties of nerve growth factor (NGF), the prototype neurotrophic substance. Neurons responsive to NGF have NGF-specific membrane receptors during the period of responsiveness. NGF increases protein and RNA synthesis; induces induction of tyrosine hydroxylase and dopamine beta-hydroxylase in sympathetic neurons and substance P in sensory neurons; promotes release of intracellular sodium and accumulation of intracellular potassium in sympathetic and sensory neurons; induces receptor mediated endocytosis; and is transported by retrograde axonal flow to the somata of responsive neurons. There are basically two forms of NGF. Beta NGF is a low (26,000) molecular weight form consisting of two 118 amino acid chains. Seven S NGF is a high (130,000) molecular weight form made up of three subunits, of which the alpha subunit is the growth promoting factor. The salivary glands appear to be exocrine organs for NGF. Non-neuronal cells in peripheral ganglia, as well as other cells, including skin fibroblasts, some sarcomas, neuroblastomas, adrenal medulla cells, C-6 glioma cells and RG-18 astrocytes, produce NGF-like substances with similar properties. NGF production can be induced in adrenal medulla and iris cells by denervation. Whether or not NGF produced by peripheral tissues is identical to NGF found in mouse submandibular glands has not been established.

Harry Goldsmith, M.D. of Dartmouth College discussed a method for providing an extraaxial blood supply to sites of potential brain and spinal cord regeneration. This is accomplished by creating intact omental flaps and routing them under the skin to the brain or spinal cord. It was claimed that by laying such flaps over the brain or spinal cord, connections were established between omental and pial vessels. It was argued that edema in spinal cord injury might be reduced by omental vascularization.

Richard Sidman, M.D. of the Harvard Medical School reviewed some of his findings on the use of synthetic guides for support of nerve regeneration. The growth of dissociated embryo spinal cord cells on glass and a plastic polymer was found to be comparable. A polyalanine polymer supported growth of both spinal cord and 7-day dissociated cerebellar cells. In peripheral nerve regeneration, the gap length between cut ends of the nerve must be within 10 mm for the segments to rejoin. In using an optic nerve model for CNS regeneration, leaving an intact retinal supply is critical. After insertion of a plastic tube guide between cut ends of nerve, tissue was found within the tube. The accretion of blood vessels preceded any neural growth. After 12 weeks, nerve fibers, some myelinated, were found within the plastic guide. The myelin was almost entirely CNS myelin. Evoked potential studies to establish conduction in these regenerated fibers were not done.

Mark Jennings, M.D. of the Massachusetts General Hospital examined the properties of teratomas as a possible source of primitive nerve cells and concluded that teratomas are not a good source for transplant material.

Barry Arnason, M.D. of the University of Chicago discussed immunological factors that would influence grafts. In early studies it was found that tumors placed in the brains of host animals survived better than tumors transplanted to other sites, laying the foundation for the concept that the CNS is an "immunologically privileged site." This concept was initially proposed by Dr. Peter Medawar, but Dr. Medawar also demonstrated that if an animal became sensitized to a tissue, and that tissue was then placed in the brain, rejection would occur. In terms of some antigens, the brain is a very potent route for immune defense mechanisms. With regard to the concept of an immunologically privileged site, neurons and glia do not have histocompatability antigens, while CNS endothelial cells do. This lack of histocompatability antigens may be the reason why transplants are not rejected, more than because the CNS is an immunologically privileged site. Lymphoid tissue has been found to share a number of antigens with the CNS. Lymphocytes have beta-adrenergic, dopamine, endorphin and acetylcholine receptors, as well as a host of others. Lymphocytes can also make ACTH, and they have receptors for ACTH. Both helper T cells and cerebellar Purkinje cells marked by OKT4, and anti-MAG (myelin-associated glycoprotein) antibody recognizes NK cells (killer T cells). There are many fundamentals about CNS transplantation that are unknown. Among other things, it is possible that the disease process for which a transplant is performed might also affect the transplanted tissue.

Albert Aguayo, M.D. of McGill University described peripheral nerve bridges for supporting CNS axon growth. *In situ*,

peripheral nervous system (PNS) neurons successfully elongate axons after axotomy, while CNS neurons do not. Regenerating central branches of dorsal root ganglia neurons grow as far as the cord, and not further, i.e. as far as the Schwann cell domain. In PNS bridges traversing medulla to spinal cord, half of the fibers therein originate from dorsal root ganglia neurons. The rest of the fibers are central axons going in both directions, i.e. some are of medullary origin and others are of spinal cord origin. The cells giving rise to the fibers are located near the graft site. As soon as the fibers enter the CNS, they stop growing, and maximum penetration is 2 mm. The PNS bridges in which the central axons grow, on the other hand, are up to 7 cm long. The size of the lesion influences the neurons that are recruited into contributing fibers - the larger the size of the lesion, the more neurons are recruited. There are indications that fibers in the bridges grow from damaged axons, and do not collaterally sprout from undamaged axons. Electrical activity has been recorded in the bridges. What is not yet known is whether meaningful messages are relayed to target cells at the other ends of the bridges. There is also no evidence yet to prove that *de novo* synapses have been formed at the distal ends of the bridges, as it has not been possible to rule out the presence of preexisting collaterals.

Carl Cotman, Ph.D. of the University of California, Irvine, reviewed studies of transplants to restore innervation to hippocampus. The septum projects cholinergic fibers to the hippocampus. If the septum is destroyed, cholinergic and other input implants can be applied. Septal implants restore cholinergic input to the hippocampus. Survival of donor cells can be altered by delay of transplantation after initial injury, and there are optimum times for transplantation of donor tissues of different ages and origins. Neurotrophic factors are found in the host tissue, within the implant cavity, and these peak at about 10 days. There is also some indication of host production of inhibitory as well as growth promoting factors. If the raphe projection to the hippocampus via the fimbria is cut, the serotoninergic input to the hippocampus can be restored by raphe implants. This input is not precise, however, and in some areas the innervation is hyperdense, which may be related to the possibility that these fibers do not form synapses.

William Freed, Ph.D. of St. Elizabeth's Hospital, Washington, D.C. presented studies on embryonic cell transplants for experimental Parkinson's disease. Rats whose substantia nigra has been lesioned unilaterally exhibit circling behavior to the side of the lesion when injected with amphetamine. This drug stimulates release of dopamine from the intact substantia nigra on the opposite side. The target tissue for dopamine (striatum) becomes supersensitive to the neurotransmitter, and thus injection of apomorphine, a dopamine agonist, produces circling behavior to the side opposite the substantia nigra lesion. Transplantation of embryonic substantia nigra cells into the region of the striatum reduces or relieves the rotatory response to amphetamine and apomorphine. On the basis of results with animal studies, it was speculated that multiple adrenal medulla grafts would be needed to produce sufficient dopamine to effect functional recovery from Parkinson's disease in man. It was emphasized that there were many unknowns about transplantation, and much information remained to be gathered from animal studies prior to transplanting human patients.

1984 VA Regeneration Research Symposium

A symposium sponsored by the Veterans Administration entitled "Neurochemistry of Regeneration" will be held at Timberline Lodge, Mount Hood, Oregon from March 9-11, 1984. The meeting, which was organized by the VA Office of Regeneration Research Programs, will be an associated symposium of the American Society for Neurochemistry, which is holding its annual meeting in Portland, Oregon from March 11-16, 1984. Invited speakers include Drs. Bernard Agranoff, Kevin Barron, Frank Collins, Carl Cotman, Jean DeVellis, Lawrence Eng, Barry Hoffer, Paul Hoffman, Robert Ledeen, Marston Manthorpe, Karina Meiri, Regino Perez-Polo, Paul Reier, Eric Shooter and Pate Skene. Abstracts of the presentations will be published in the next edition of this newsletter.

Editorial Change

Dr. Jerald J. Bernstein has resigned his post as editor of the VA Regeneration Research Newsletter because of the burden of other committments. The editorial duties of the Newsletter will be assumed by Dr. Fredrick J. Seil, Director of the VA Office of Regeneration Research Programs.

We are grateful to Dr. Bernstein for the initiation of the Newsletter, and for having overseen publication of the first two issues. His policy of publishing negative results, methodology communications and short reviews and articles, as announced in the first issue (July, 1982) of the Newsletter, will be continued. Readers are reminded to submit such communications. The Newsletter will be published biannually.

Please address all future correspondence to:

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Office of General Counsel Washington D.C. 20420

Veterans Administration

JUN 4 1984

In Reply Refer To: (02C)

Honorable John Paul Hammerschmidt
House of Representatives
Washington, D.C. 20515

Dear Mr. Hammerschmidt:

Enclosed is a copy of the Agency's response to the questions you submitted following the hearing held on April 26, 1984, on medical research.

Thank you for this opportunity to provide additional information for the record.

Sincerely yours,

JOHN P. MURPHY
General Counsel

Enclosure

Question: As the Ranking Member of the House Committee on Aging, I am vitally interested in research on Alzheimer's Disease. On page 5 of the statement of Dr. Kenneth Davis he mentions that a research study he had been making can only be done through the cooperative studies program of the Veterans Administration. Would you please briefly expand on this statement for it certainly indicates the importance of VA medicine in research activities on a very significant national problem?

Answer: The VA cooperative studies program is a unique national resource in that it provides a cost effective mechanism for carrying out large scale clinical trials that require significant numbers of patients for a definitive result. The cooperative studies program provides the organizational and scientific expertise to allow pooling of data from patients who have undergone alternative treatments for a given illness under controlled clinical conditions, with careful attention to the protection of patients' rights. Thus patient data from a set of VA hospitals can be merged to provide important new information of the usefulness of medical and surgical diagnostic procedures and treatments. Linking this research effort to the patient care function of the VA medical care system is unique and provides efficient use of resources to gain vital new knowledge of the effectiveness of medical procedures.

Question: You state that the subject of the hearings of April 26 have priority status in the VA research program. Please tell us how you make determinations as to priorities within your total appropriation?

Answer: Research areas are designated as high priority after analysis of both the incidence of a medical condition among veteran patients cared for in VA medical centers and the likelihood that a special research initiative may advance the state of the art of diagnosis and/or treatment of the condition. Such analyses are carried on by Medical Research Service in an ongoing process that includes:

1. Review of the incidence of illness patterns among patients cared for in VA facilities.
2. Consultation with leading clinical and research scientists on promising areas for research concentration (e.g. members of Medical Research Service Merit Review Committees, Program Specialists and special ad hoc committees convened to analyze research opportunities in specific fields).

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